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(54) Title: ALBUMIN FUSION PROTEINS

(57) Abstract: The present invention encompasses albumin fusion proteins. Nucleic acid molecules encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Additionally the present invention encompasses pharmaceutical compositions comprising albumin fusion proteins and methods of treating or preventing diseases, disorders or conditions related to diabetes mellitus using albumin fusion proteins of the invention.

Albumin Fusion Proteins

BACKGROUND OF THE INVENTION

[0001] The invention relates generally to Therapeutic proteins (including, but not limited to, at least one polypeptide, antibody, peptide, or fragment and variant thereof) fused to albumin or fragments or variants of albumin. The invention encompasses polynucleotides encoding therapeutic albumin fusion proteins, therapeutic albumin fusion proteins, compositions, pharmaceutical compositions, formulations and kits. Host cells transformed with the polynucleotides encoding therapeutic albumin fusion proteins are also encompassed by the invention, as are methods of making the albumin fusion proteins of the invention using these polynucleotides, and/or host cells.

[0002] Over the past few decades, an increasing percentage of the population has become diabetic. Diabetes mellitus is categorized into two types: Type I, known as Insulin-Dependent Diabetes Mellitus (IDDM), or Type II, known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM). IDDM is an autoimmune disorder in which the insulin-secreting pancreatic beta cells of the islets of Langerhans are destroyed. In these individuals, recombinant insulin therapy is employed to maintain glucose homeostasis and normal energy metabolism. NIDDM, on the other hand, is a polygenic disorder with no one gene responsible for the progression of the disease.

[0003] In NIDDM, insulin resistance eventually leads to the abolishment of insulin secretion resulting in insulin deficiency. Insulin resistance, at least in part, ensues from a block at the level of glucose uptake and phosphorylation in humans. Diabetics demonstrate a decrease in expression in adipose tissue of insulin-receptor substrate 1 ("IRS1") (Carvalho et al., FASEB J 13(15):2173-8 (1999)), glucose transporter 4 ("GLUT4") (Garvey et al., Diabetes 41(4):465-75 (1992)), and the novel abundant protein M gene transcript 1 ("apM1") (Statnick et al., Int. J. Exp. Diabetes 1(2):81-8 (2000)), as well as other as of yet unidentified factors. Insulin deficiency in NIDDM leads to failure of normal pancreatic beta-cell function and eventually to pancreatic-beta cell death.

[0004] Insulin affects fat, muscle, and liver. Insulin is the major regulator of energy metabolism. Malfunctioning of any step(s) in insulin secretion and/or action can lead to many disorders, including for example the dysregulation of oxygen utilization,

adipogenesis, glycogenesis, lipogenesis, glucose uptake, protein synthesis, thermogenesis, and maintenance of the basal metabolic rate. This malfunctioning results in diseases and/or disorders that include, but are not limited to, hyperinsulinemia, insulin resistance, insulin deficiency, hyperglycemia, hyperlipidemia, hyperketonemia, and diabetes.

[0005] Numerous debilitating diabetes-related secondary effects include, but are not limited to, obesity, forms of blindness (cataracts and diabetic retinopathy), limb amputations, kidney failure, fatty liver, coronary artery disease, and neuropathy.

[0006] Some of the current drugs used to treat insulin resistance and/or diabetes (e.g., insulin secratogogues – sulfonylurea, insulin sensitizers – thiazolidenediones and metformin, and α-glucosidase and lipase inhibitors) are inadequate due to the dosage amounts and frequency with which they have to be administered as a result of poor pharmacokinetic properties, the lack of effective control over blood sugar levels, and potential side effects, among other reasons. Diabetes Therapeutic proteins in their native state or when recombinantly produced exhibit a rapid *in vivo* clearance. Typically, significant amounts of therapeutics are required to be effective during therapy. In addition, small molecules smaller than the 20 kDa range can be readily filtered through the renal tubules (glomerulus) leading to dose-dependent nephrotoxicity.

[0007] Diabetes Therapeutic proteins in their native state or when recombinantly produced are typically labile molecules exhibiting short shelf-lives, particularly when formulated in aqueous solutions. The instability in these molecules when formulated for administration dictates that many of the molecules must be lyophilized and refrigerated at all times during storage, thereby rendering the molecules difficult to transport and/or store. Storage problems are particularly acute when pharmaceutical formulations must be stored and dispensed outside of the hospital environment. Many protein and peptide drug compositions also require the addition of high concentrations of other protein such as albumin to reduce or prevent loss of protein due to binding to the container. For this reason, many therapeutic proteins are formulated in combination with a large proportion of albumin carrier molecule (100-1000 fold excess), though this is an undesirable and expensive feature of the formulation.

[0008] Few practical solutions to the storage problems of labile protein molecules have been proposed. Accordingly, there is a need for stabilized, long lasting formulations of proteinaceous therapeutic molecules that are easily dispensed, preferably with a simple

formulation requiring minimal post-storage manipulation.

[0009] Human serum albumin possesses many desirable characteristics. HSA is found throughout the body, but more specifically in the interstitial space and in blood at serum concentrations of 40 g/L which is equivalent to 0.7 mM (Yeh et al., Proc. Natl. Acad. Sci. USA, 89:1904-1908 (1992)). HSA is considered to be the most abundant protein of the serum and is responsible for maintaining osmolarity. HSA has favorable pharmacokinetic properties and is cleared very slowly by the liver displaying *in vivo* half-lives up to several weeks (Yeh et al., Proc. Natl. Acad. Sci. USA, 89:1904-1908 (1992); Waldmann, T.A., Albumin Structure, Function and Uses, pp. 255-273 (1977)). HSA lacks enzymatic activity and antigenicity thereby eliminating potentially undesirable side effects. HSA acts as a carrier for endogenous as well as exogenous ligands. Combined, these features can be extended, at least partially, onto albumin fusion proteins. The poor pharmacokinetic properties displayed by Diabetes Therapeutic proteins can then be circumvented.

[0010] Human serum albumin (HSA, or HA), a protein of 585 amino acids in its mature form (SEQ ID NO:327) of approximately 66 kDa, is responsible for a significant proportion of the osmotic pressure of serum and also functions as a carrier of endogenous and exogenous ligands. At present, HA for clinical use is produced by extraction from human blood. The production of recombinant HA (rHA) in microorganisms has been disclosed in EP 330 451 and EP 361 991.

[0011] The present invention is directed to albumin fusion proteins comprising a Therapeutic protein (e.g., a polypeptide, antibody, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin. The present invention also encompasses polynucleotides comprising, or alternatively consisting of, nucleic acid molecules encoding a Therapeutic protein (e.g., a polypeptide, antibody, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin that is sufficient to prolong the shelf life of the Therapeutic protein, increase serum half-life, and/or stabilize the Therapeutic protein and/or its activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo*. In one embodiment, an albumin fusion protein encoded by a polynucleotide described in Table 1 or 2 has extended shelf life. In a second embodiment, an albumin fusion protein encoded by a polynucleotide described in Table 1 or 2 has a longer serum half-life and/or stabilized activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo* than the corresponding

unfused Therapeutic molecule described in Table 1 or 2. The present invention also encompasses polynucleotides, comprising, or alternatively consisting of, nucleic acid molecules encoding proteins comprising a Therapeutic protein (e.g., a polypeptide, antibody, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin. Albumin fusion proteins encoded by polynucleotides of the invention are also encompassed by the invention, as are host cells containing these polynucleotides, and methods of making the albumin fusion proteins of the invention and using these polynucleotides, and/or host cells. The invention also encompasses polynucleotides encoding therapeutic albumin fusion proteins, therapeutic albumin fusion proteins, compositions, pharmaceutical compositions, formulations and kits.

SUMMARY OF THE INVENTION

[0012] In a preferred embodiment, the albumin fusion protein of the invention comprises one or more of the Therapeutic proteins disclosed in the "Therapeutic Protein: X" column of Table 1. Fusion proteins comprising fragments or variants of one or more of the Therapeutic proteins as disclosed in the "Construct Name" column of Table 2 are also encompassed by the invention. Polynucleotides comprising, or alternatively consisting of, nucleic acid molecules encoding the above albumin fusion proteins are also encompassed by the invention, as are host cells containing these polynucleotides. In one embodiment, an albumin fusion protein encoded by a polynucleotide described in Table 1 or 2 has extended shelf life. In a second embodiment, an albumin fusion protein encoded by a polynucleotide described in Table 1 or 2 has a longer serum half-life and/or stabilized activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo* than the corresponding unfused Therapeutic molecule described in Table 1.

[0013] In a preferred aspect of the invention, albumin fusion proteins include, but are not limited to, those encoded by the polynucleotides described in Table 2.

[0014] The invention also encompasses pharmaceutical formulations comprising an albumin fusion protein of the invention and a pharmaceutically acceptable diluent or carrier. Such formulations may be in a kit or container. Such kit or container may be packaged with instructions pertaining to the extended shelf life of the Therapeutic protein. Such formulations may be used in methods of treating (e.g., ameliorating) preventing, or diagnosing a disease or disease symptom in a patient, preferably a mammal, most

preferably a human, comprising the step of administering the pharmaceutical formulation to the patient.

[0015] In other embodiments, the present invention encompasses methods of preventing or treating (e.g., ameliorating) a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indication Y" column of Table 1 comprising administering to a patient in which such treatment or prevention is desired an albumin fusion protein of the invention that comprises a Therapeutic protein portion corresponding to a Therapeutic protein (or fragment or variant thereof) disclosed in the "Therapeutic Protein: X" column of Table 1 (in the same row as the disease or disorder to be treated is listed in the "Preferred Indication Y" column of Table 1) in an amount effective to treat (e.g., ameliorate) or prevent the disease or disorder. Moreover, diseases or disorders that can be treated or prevented with an albumin fusion protein of the invention include, but are not limited to, diabetes (e.g., Non-Insulin-Dependent Diabetes Mellitus (NIDDM) or Insulin-Dependent Diabetes Mellitus (IDDM)), insulin resistance, insulin deficiency, hyperinsulinemia, hyperglycemia, dyslipidemia, hyperlipidemia, hyperketonemia, hypertension, coronary artery disease, atherosclerosis, renal failure, neuropathy (e.g., autonomic neuropathy, parasympathetic neuropathy, and polyneuropathy), retinopathy, cataracts, metabolic disorders (e.g., insulin and/or glucose metabolic disorders), endocrine disorders, obesity, weight loss, liver disorders (e.g., liver disease, cirrhosis of the liver, and disorders associated with liver transplant), and conditions associated with these diseases or disorders.

[0016] In one embodiment, an albumin fusion protein described in Table 1 or 2 has extended shelf life.

[0017] In a second embodiment, an albumin fusion protein described in Table 1 or 2 is more stable than the corresponding unfused Therapeutic molecule described in Table 1.

[0018] In another preferred embodiment, the "Therapeutic protein" is a protein that is useful to treat (e.g., ameliorate) or prevent a metabolic/endocrine disorder. In a highly preferred embodiment, the metabolic/endocrine disorder is diabetes and/or a condition associated with diabetes. As a non-limiting example, a "Therapeutic protein" may be one that regulates glucose uptake by cells, that binds specifically to a particular cell type (e.g., normal adipocytes, myotubes, hepatocytes, and pancreatic beta cells of the Islet of

Langerhans, and/or abnormal (e.g., cancer cell or insulin-resistant adipocytes, myotubes, and hepatocytes)), that enhances insulin sensitivity in insulin-responsive tissues, and/or that regulates hepatic glucose output, and therefore may be used to target a compound (drug, or cytotoxic agent) to that cell type specifically.

[0019] In highly preferred embodiments, the present invention encompasses methods of preventing or treating (e.g., ameliorating) diabetes and/or a condition associated with diabetes comprising administering to a patient (preferably a human) in which such prevention or treatment is desired an albumin fusion protein of the invention that comprises a Therapeutic protein portion corresponding to a Therapeutic protein (or fragment or variant thereof) disclosed in the "Therapeutic Protein: X" column of Table 1 in an amount effective to treat or prevent diabetes and/or a condition associated with diabetes. Conditions associated with diabetes that can be prevented or treated with an albumin fusion protein of the invention include, but are not limited to, hyperglycemia, obesity, diabetic retinopathy, mononeuropathy, polyneuropathy, atherosclerosis, ulcers, heart disease, stroke, anemia, gangrene (e.g., of the feet and hands), impotence, infection, cataract, poor kidney function, malfunctioning of the autonomic nervous system, impaired white blood cell function, Carpal tunnel syndrome, Dupuytren's contracture, and diabetic ketoacidosis.

[0020] In a most preferred embodiment, an albumin fusion protein of the invention is administered to a patient to modulate or maintain glucose homeostasis.

[0021] In other embodiments, the present invention encompasses a method of maintaining a basal level of insulin in a patient comprising administering an albumin fusion protein of the invention.

[0022] The invention also relates to methods of regulating (e.g., suppressing or decreasing) appetite, and methods of altering nutritional partitioning in a patient (e.g., methods of increasing muscle mass and/or methods of decreasing fat mass) comprising administering to a patient (preferably a human) an albumin fusion protein of the invention.

[0023] The invention also relates to methods of treating or preventing insulin- related disorders comprising administering to a patient (preferably a human) an albumin fusion protein of the invention.

[0024] The invention further relates to methods of regulating insulin responsiveness in a patient, as well as methods of increasing glucose uptake by a cell, and methods of

regulating insulin sensitivity of a cell, using the albumin fusion proteins of the invention.

[0025] The albumin fusion proteins of the invention may be administered alone or in combination with other Therapeutic proteins or molecules (e.g., insulin and/or other proteins (including antibodies), peptides, or small molecules that regulate insulin sensitivity, weight, heart disease, hypertension, neuropathy, cell metabolism, and/or glucose, insulin, or other hormone levels, in a patient). In specific embodiments, the albumin fusion proteins of the invention are administered in combination with insulin (or an insulin derivative, analog, fusion protein, or secretagogue).

[0026] The present invention further includes transgenic organisms modified to contain or express compositions of the invention (including, but not limited to, fusion proteins and/or the polynucleotides described in Tables 1 and 2), preferably modified to express an albumin fusion protein of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0027] Figure 1 depicts the ability of GLP-1 albumin fusion proteins and exendin-4 albumin fusion proteins to enhance glucose sensitivity and uptake into 3T3-L1 adipocytes as compared to GLP-1 and exendin-4 alone, respectively.

[0028] Figure 2 shows the effectiveness of insulin albumin fusion proteins (CID 2250 and 2276) to allow for glucose uptake into 3T3-L1 adipocytes.

[0029] Figure 3 is a map of the vector pPPC0005 cloning vector (ATCC Deposit Number PTA-3278).

[0030] Figure 4 is a map of the pSAC35 yeast *S. Cerevisiae* expression vector (Sleep *et al.*, Biotechnology 8:42 (1990)).

[0031] Figure 5A-D shows the amino acid sequence of the mature form of human albumin (SEQ ID NO:327) and a polynucleotide encoding it (SEQ ID NO:326).

[0032] Figure 6 shows the effect of various dilutions of IFNb albumin fusion proteins encoded by DNA comprised in CID 2011 and 2053 on SEAP activity in the ISRE-

SEAP/293f reporter cells (see Example 19). Proteins were serially diluted from 5e-7 to 1e-14 g/ml in DMEM/10% FBS and used to treat ISRE-SEAP/293f reporter cells. After 24 hours supernatants were removed from reporter cells and assayed for SEAP activity. IFNb albumin fusion protein was purified from three stable clones: 293f/#2011, CHO/#2011 and NS0/#2053. Mammalian derived IFNb, Avonex, came from Biogen and was reported to have a specific activity of 2.0e5 IU/ug.

[0033] Figure 7 illustrates the steady-state levels of insulin mRNA in INS-1 (832/13) cells after treatment with GLP-1 or GLP-1 albumin fusion protein encoded by construct ID 3070 (CID 3070 protein). Both GLP-1 and the CID 3070 protein stimulate transcription of the insulin gene in INS-1 cells. The first bar (black) represents the untreated cells. Bars 2-4 (white) represent cells treated with the indicated concentrations of GLP-1. Bars 5-7 (gray) represent cells treated with the indicated concentrations of CID 3070 protein.

[0034] Figure 8 compares the anti-proliferative activity of IFN albumin fusion protein encoded by CID 3165 (CID 3165 protein) and recombinant IFNa (rIFNa) on Hs294T melanoma cells. The cells were cultured with varying concentrations of either CID 3165 protein or rIFNa and proliferation was measured by BrdU incorporation after 3 days of culture. CID 3165 protein caused measurable inhibition of cell proliferation at concentrations above 10 ng/ml with 50% inhibition achieved at approximately 200 ng/ml. (■) = CID 3165 protein, (◆) = rIFNa.

[0035] Figure 9 shows the effect of various dilutions of IFNa albumin fusion proteins on SEAP activity in the ISRE-SEAP/293F reporter cells. One preparation of IFNa fused upstream of albumin (◆) was tested, as well as two different preparations of IFNa fused downstream of albumin (▲) and (■).

[0036] Figure 10 shows the effect of time and dose of IFNa albumin fusion protein encoded by DNA comprised in construct 2249 (CID 2249 protein) on the mRNA level of OAS (p41) in treated monkeys (see Example 92). Per time point: first bar = Vehicle control, 2nd bar = 30 ug/kg CID 2249 protein day 1 iv, third bar = 30 ug/kg CID 2249 protein day 1 sc, 4th bar = 300 ug/kg CID 2249 protein day 1 sc, 5th bar = 40 ug/kg

recombinant IFNa day 1, 3 and 5 sc.

DETAILED DESCRIPTION

Definitions

[0037] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[0038] As used herein, "polynucleotide" refers to a nucleic acid molecule having a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:Y (wherein Y is a number shown in column 6 of Table 2) or a fragment or variant thereof; a nucleotide sequence generated as described in Table 2 or in the Examples; a nucleotide sequence contained in an albumin fusion construct described in Table 2; a nucleotide sequence contained in an albumin fusion construct deposited with the ATCC (as described in Table 3); and/or more generally to a nucleotide sequence encoding a Therapeutic albumin fusion protein of the invention. Also as used herein, "polynucleotide" refers to a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one Therapeutic protein X (or fragment or variant thereof); a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NO:Y (as described in column 6 of Table 2) or a fragment or variant thereof; a nucleic acid molecule having a nucleotide sequence comprising or alternatively consisting of the sequence shown in SEQ ID NO:X; a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NO:Z; a nucleic acid molecule having a nucleotide sequence encoding an albumin fusion protein of the invention generated as described in Table 2 or in the Examples; a nucleic acid molecule having a nucleotide sequence encoding a Therapeutic albumin fusion protein of the invention, a nucleic acid molecule having a nucleotide sequence contained in an albumin fusion construct described in Table 2.

[0039] As used herein, "albumin fusion construct" refers to: a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide

encoding at least one molecule of a Therapeutic protein of the invention (including fragments and variants); a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein of the invention (including fragments and variants) generated as described in Table 2 or in the Examples; and/or a nucleic acid molecule comprising, or alternatively consisting of, one or more of the above polynucleotides and further comprising, or alternatively consisting of, one or more of the following: (1) a functional self-replicating vector (including but not limited to, a shuttle vector, an expression vector, an integration vector, and/or a replication system), (2) a region for initiation of transcription (e.g., a promoter region, such as for example, a regulatable or inducible promoter, a constitutive promoter), (3) a region for termination of transcription, (4) a leader sequence, and (5) a selectable marker. The polynucleotide encoding the Therapeutic protein and albumin protein, once part of the albumin fusion construct, may each be referred to herein as a "portion," "region" or "moiety" of the albumin fusion construct.

[0040] As used herein, "mature albumin fusion protein" refers to: the processed form of an albumin fusion protein. An albumin fusion protein of the invention is processed by a host cell and secreted into the surrounding culture medium. Processing of the nascent albumin fusion protein that occurs in the secretory pathways of the host used for expression may include, but is not limited to signal peptide cleavage; formation of disulfide bonds; proper folding; addition and processing of carbohydrates (such as for example, N- and O- linked glycosylation); specific proteolytic cleavages; and assembly into multimeric proteins. An albumin fusion protein of the invention is preferably in the processed form. In a most preferred embodiment, the "processed form of an albumin fusion protein" refers to an albumin fusion protein product which has undergone N-terminal signal peptide cleavage, herein also referred to as a "mature albumin fusion protein".

[0041] The present invention relates generally to polynucleotides encoding albumin fusion proteins; albumin fusion proteins; and methods of treating (e.g,. ameliorating) or preventing a disease or disorder using albumin fusion proteins or polynucleotides encoding albumin fusion proteins of the invention. As used herein, "albumin fusion protein" refers

to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a Therapeutic protein (or fragment or variant thereof). In preferred embodiments, the present invention relates to treating (e.g., ameliorating) or preventing a metabolic/endocrine disorder using a polynucleotide and/or albumin fusion protein of the invention. In highly preferred embodiments, the present invention relates to a method of treating or preventing diabetes and/or a condition associated with diabetes using a polynucleotide and/or albumin fusion protein of the invention. In a highly preferred embodiment, an albumin fusion protein of the invention comprises at least one molecule of a Therapeutic protein X or fragment or variant of thereof (including, but not limited to a mature form of the Therapeutic protein X) and at least one molecule of albumin or fragment or variant thereof (including but not limited to a mature form of albumin).

[0042] As used herein, "albumin fusion protein" refers to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a Therapeutic protein (or fragment or variant thereof). An albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion (i.e., the albumin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a Therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of albumin). The Therapeutic protein and albumin protein, once part of the albumin fusion protein, may each be referred to herein as a "portion", "region" or "moiety" of the albumin fusion protein (e.g., a "Therapeutic protein portion" or an "albumin protein portion").

[0043] An additional embodiment includes a protein containing at least one protein, fragment, or variant of a Therapeutic protein of the invention and at least a protein fragment or variant of human serum albumin, which are associated with one another, via chemical conjugation.

[0044] In several instances, a representative clone containing an albumin fusion construct of the invention was deposited with the American Type Culture Collection (herein referred to as "ATCC®"). Furthermore, it is possible to retrieve a given albumin fusion construct from the deposit by techniques known in the art and described elsewhere herein. The ATCC® is located at 10801 University Boulevard, Manassas, Virginia 20110-

2209, USA. The ATCC® deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0045] In one embodiment, the invention provides a polynucleotide encoding an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin protein. In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin protein. In a preferred embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin protein encoded by a polynucleotide described in Table 2. In a further preferred embodiment, the invention provides a polynucleotide encoding an albumin fusion protein whose sequence is shown as SEQ ID NO:Y in Table 2. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a Therapeutic protein and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active variant of a Therapeutic protein and a serum albumin protein. In preferred embodiments, the serum albumin protein component of the albumin fusion protein is the mature portion of serum albumin. The invention further encompasses polynucleotides comprising, or alternatively consisting of, nucleic acid molecules and host cells containing these nucleic acids encoding these albumin fusion proteins.

[0046] In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein, and a biologically active and/or therapeutically active fragment of serum albumin. In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a biologically active and/or therapeutically active variant of serum albumin. In preferred embodiments, the Therapeutic protein portion of the albumin fusion protein is the mature portion of the Therapeutic protein. In a further preferred embodiment, the Therapeutic protein portion of the albumin fusion protein is the extracellular soluble domain of the Therapeutic protein. In an alternative embodiment, the Therapeutic protein portion of the albumin fusion protein is the active form of the Therapeutic protein. The invention further encompasses polynucleotides comprising, or alternatively consisting of,

nucleic acid molecules encoding the albumin fusion proteins of the invention. Host cells containing these polynucleotides are also encompassed by the invention as are methods of making albumin fusion proteins using these host cells.

[0047] In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment or variant of a Therapeutic protein and a biologically active and/or therapeutically active fragment or variant of serum albumin. In a preferred embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, the mature portion of a Therapeutic protein and the mature portion of serum albumin. The invention further encompasses polynucleotides comprising, or alternatively consisting of, nucleic acid molecules encoding the albumin fusion proteins of the invention. Host cells containing these polynucleotides are also encompassed by the invention as are methods of making albumin fusion proteins using these host cells.

Therapeutic proteins

[0048] As stated above, a polynucleotide of the invention encodes a protein comprising or alternatively consisting of, at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion.

[0049] As used herein, "Therapeutic protein" refers to proteins, polypeptides, antibodies, peptides or fragments or variants thereof, having one or more therapeutic and/or biological activities. Therapeutic proteins encompassed by the invention include but are not limited to, proteins, polypeptides, peptides, antibodies, and biologics. (The terms peptides, proteins, and polypeptides are used interchangeably herein.) It is specifically contemplated that the term "Therapeutic protein" encompasses antibodies and fragments and variants thereof. Thus a protein of the invention may contain at least a fragment or variant of a Therapeutic protein, and/or at least a fragment or variant of an antibody. Additionally, the term "Therapeutic protein" may refer to the endogenous or naturally occurring correlate of a Therapeutic protein.

[0050] By a polypeptide displaying a "therapeutic activity" or a protein that is "therapeutically active" is meant a polypeptide that possesses one or more known biological and/or therapeutic activities associated with a therapeutic protein such as one or

more of the Therapeutic proteins described herein or otherwise known in the art. In a preferred embodiment, the "Therapeutic protein" is a protein that is useful to treat (ameliorate) or prevent a metabolic/endocrine disorder. As a non-limiting example, a "Therapeutic protein" may be one that binds specifically to a particular cell type (normal (e.g., lymphocytes) or abnormal e.g., (cancer cells)) and therefore may be used to target a compound (drug, or cytotoxic agent) to that cell type specifically.

[0051] In a highly preferred embodiment, the metabolic/endocrine disorder is diabetes mellitus and/or one or more conditions associated with diabetes. In preferred embodiments, the "Therapeutic protein" is a protein that is useful to treat (e.g., ameliorate) or prevent Type II Non-Insulin-Dependent Diabetes Mellitus (NIDDM) and/or a condition or conditions associated with NIDDM. In other preferred embodiments, the "Therapeutic protein" is a protein that is useful to treat (e.g., ameliorate) or prevent Type I Insulin-Dependent Diabetes Mellitus (IDDM) and/or a condition or conditions associated with IDDM. In other preferred embodiments, the "Therapeutic protein" is a protein that is useful to treat (e.g., ameliorate) or prevent a condition including, but not limited to, hyperglycemia, obesity, diabetic retinopathy, mononeuropathy, polyneuropathy, atherosclerosis, ulcers, heart disease, stroke, anemia, gangrene (e.g. of the feet and hands), impotence, infection, cataract, poor kidney function, malfunctioning of the autonomic nervous system, impaired white blood cell function, Carpal tunnel syndrome, Dupuytren's contracture, and diabetic ketoacidosis.

[0052] As a non-limiting example, a "Therapeutic protein" may be one that regulates glucose uptake by cells and/or that binds specifically to a particular cell type (e.g., normal adipocytes, myotubes, hepatocytes, and pancreatic beta cells of the Islet of Langerhans, and/or abnormal (e.g., cancer cell or insulin-resistant adipocytes, myotubes, and hepatocytes)), that enhances insulin sensitivity in insulin-responsive tissues, and/or that regulates hepatic glucose output, and therefore may be used to target a compound (drug, or cytotoxic agent) to that cell type specifically.

[0053] For example, a non-exhaustive list of "Therapeutic protein" portions which may be comprised by an albumin fusion protein of the invention includes, but is not limited to, proteins comprising, a polypeptide having an amino acid sequence disclosed in Table 2, column 8 as SEQ ID NO: Z and fragments or variants thereof; or in Table 1, column 1 as "Therapeutic Protein X" and fragments and variants thereof.

[0054] Interferon hybrids may also be fused to the amino or carboxy terminus of albumin to form an interferon hybrid albumin fusion protein. Interferon hybrid albumin fusion protein may have enhanced, or alternatively, suppressed interferon activity, such as antiviral responses, regulation of cell growth, and modulation of immune response (Lebleu et al., *PNAS* USA, 73:3107-3111 (1976); Gresser et al., *Nature*, 251:543-545 (1974); and Johnson, *Texas Reports Biol Med*, 35:357-369 (1977)). Each interferon hybrid albumin fusion protein can be used to treat, prevent, or ameliorate viral infections (*e.g.*, hepatitis (*e.g.*, HCV); or HIV), multiple sclerosis, or cancer.

[0055] In one embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon alpha-interferon alpha hybrid (herein referred to as an alpha-alpha hybrid). For example, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha D. In a further embodiment, the A/D hybrid is fused at the common BglII restriction site to interferon alpha D, wherein the N-terminal portion of the A/D hybrid corresponds to amino acids 1-62 of interferon alpha A and the C-terminal portion corresponds to amino acids 64-166 of interferon alpha D. For example, this A/D hybrid would comprise the amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL
HEMIQQIFNLFTTKDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLM
NX$_2$DSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE

(SEQ ID NO:472), wherein the X_1 is R or K and the X_2 is A or V (see, for example, Construct ID #2875). In an additional embodiment, the A/D hybrid is fused at the common PvuIII restriction site, wherein the N-terminal portion of the A/D hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha D. For example, this A/D hybrid would comprise the amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL
HEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVMQEERVGETPLM
NX$_2$DSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE

(SEQ ID NO:457), wherein the X_1 is R or K and the X_2 is A or V (see, for example, Construct ID #2872). These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety.

[0056] In an additional embodiment, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha F. In a further embodiment, the A/F hybrid is fused at the common PvuIII restriction site, wherein the N-terminal portion of the A/F hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha F. For example, this A/F hybrid would comprise the amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRXISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL
HEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDMEACVIQEVGVEETPLM
NVDSILAVKKYFQRITLYLTEKKYSPCAWEVVRAEIMRSFSLSKIFQERLRRKE

(SEQ ID NO:467), wherein X is either R or K (see, for example, Construct ID #2874). These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety. In a further embodiment, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha B. In an additional embodiment, the A/B hybrid is fused at the common PvuIII restriction site, wherein the N-terminal portion of the A/B hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha B. For example, this A/B hybrid would comprise an amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL
HEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEX$_2$X$_3$X$_4$X$_5$QEVGVIESPL
MYEDSILAVRKYFQRITLYLTEKKYSSCAWEVVRAEIMRSFSLSINLQKRLKSKE

(SEQ ID NO:462), wherein the X_1 is R or K and X_2 through X_5 is SCVM or VLCD (see, for example, Construct ID #2873). These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety.

[0057] In another embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon beta-interferon alpha hybrid (herein referred to as a beta-alpha hybrid). For example, the beta-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon beta-1 fused to interferon alpha D (also referred to as interferon alpha-1).

[0058] In a further embodiment, the beta-1/alpha D hybrid is fused wherein the N-terminal portion corresponds to amino acids 1-73 of interferon beta-1 and the C-terminal

portion corresponds to amino acids 74-167 of interferon alpha D. For example, this beta-1/alpha D hybrid would comprise an amino acid sequence:
MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDA
ALTIYEMLQNIFAIFRQDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGET
PLMNXDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRK
E (SEQ ID NO:823), wherein X is A or V. These hybrids are further described in U.S. Patent No. 4,758,428, which is hereby incorporated by reference in its entirety.

[0059] In another embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon alpha-interferon beta hybrid (herein referred to as a alpha-beta hybrid). For example, the alpha-beta hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha D (also referred to as interferon alpha-1) fused to interferon beta-1. In a further embodiment, the alpha D/beta-1 hybrid is fused wherein the N-terminal portion corresponds to amino acids 1-73 of interferon alpha D and the C-terminal portion corresponds to amino acids 74-166 of interferon beta-1. For example, this alpha D/beta-1 hybrid would have an amino acid sequence:
MCDLPETHSLDNRRTLMLLAQMSRISPSSCLMDRHDFGFPQEEFDGNQFQKAPAIS
VLHELIQQIFNLFTTKDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTR
GKLMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN
(SEQ ID NO:824). These hybrids are further described in U.S. Patent No. 4,758,428, which is hereby incorporated by reference in its entirety.

[0060] In further embodiments, the interferon hybrid portion of the interferon hybrid albumin fusion proteins may comprise additional combinations of alpha-alpha interferon hybrids, alpha-beta interferon hybrids, and beta-alpha interferon hybrids. In additional embodiments, the interferon hybrid portion of the interferon hybrid albumin fusion protein may be modified to include mutations, substitutions, deletions, or additions to the amino acid sequence of the interferon hybrid. Such modifications to the interferon hybrid albumin fusion proteins may be made, for example, to improve levels of production, increase stability, increase or decrease activity, or confer new biological properties.

[0061] The above-described interferon hybrid albumin fusion proteins are encompassed by the invention, as are host cells and vectors containing polynucleotides encoding the polypeptides. In one embodiment, a interferon hybrid albumin fusion protein encoded by a

polynucleotide as described above has extended shelf life. In an additional embodiment, a interferon hybrid albumin fusion protein encoded by a polynucleotide described above has a longer serum half-life and/or more stabilized activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo* than the corresponding unfused interferon hybrid molecule.

[0062] In another non-limiting example, a "Therapeutic protein" is a protein that has a biological activity, and in particular, a biological activity. A non-exhaustive list of biological activities that may be possessed by a Therapeutic protein includes, inducing pancreatic ductal epithelial cell differentiation into insulin-secreting pancreatic beta cells, stimulating synthesis and release of insulin, enhancing glucose sensitivity, enhancing insulin sensitivity, maintaining metabolic homeostasis, regulating the activation of the complement system, enhancing or suppressing an immune response, promoting or inhibiting angiogenesis, regulating hematopoietic functions, stimulating nerve growth, or any one or more of the biological activities described herein (e.g., in the "Biological Activities" section below and/or as disclosed for a given Therapeutic protein in Table 1).

[0063] As used herein, "therapeutic activity" or "activity" may refer to an activity whose effect is consistent with a desirable therapeutic outcome in humans, or to desired effects in non-human mammals or in other species or organisms. Therapeutic activity may be measured *in vivo* or *in vitro*. For example, a desirable effect may be assayed in cell culture. As an example, the ability of a Therapeutic protein and/or albumin fusion protein of the invention (including fragments and variants thereof) to regulate glucose uptake may be routinely assayed using, or routinely modified, techniques described herein (e.g., Example 28) or otherwise known in the art. In another example, the ability of a Therapeutic protein and/or albumin fusion protein of the invention (including fragments and variants thereof) to promote expression of the H4IIe–SEAP reporters may be routinely assayed using, or routinely modified, techniques described herein (e.g., Example 35) or otherwise known in the art. Such *in vitro* or cell culture assays are known for many Therapeutic proteins. Additional example of assays include, but are not limited to, those described herein in the Examples section or in the "Exemplary Activity Assay" column of Table 1.

[0064] Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention, such as cell surface and secretory proteins, are

often modified by the attachment of one or more oligosaccharide groups. The modification, referred to as glycosylation, can dramatically affect the physical properties of proteins and can be important in protein stability, secretion, and localization. Glycosylation occurs at specific locations along the polypeptide backbone. There are usually two major types of glycosylation: glycosylation characterized by O-linked oligosaccharides, which are attached to serine or threonine residues; and glycosylation characterized by N-linked oligosaccharides, which are attached to asparagine residues in an Asn-X-Ser/Thr sequence, where X can be any amino acid except proline. N-acetylneuramic acid (also known as sialic acid) is usually the terminal residue of both N-linked and 0-linked oligosaccharides. Variables such as protein structure and cell type influence the number and nature of the carbohydrate units within the chains at different glycosylation sites. Glycosylation isomers are also common at the same site within a given cell type.

[0065] For example, several types of human interferon are glycosylated. Natural human interferon-α2 is O-glycosylated at threonine 106, and N-glycosylation occurs at asparagine 72 in interferon-α14 (Adolf *et al.*, J. Biochem 276:511 (1991); Nyman TA *et al.*, J. Biochem 329:295 (1998)). The oligosaccharides at asparagine 80 in natural interferon-β1α may play an important factor in the solubility and stability of the protein, but may not be essential for its biological activity. This permits the production of an unglycosylated analog (interferon-β1b) engineered with sequence modifications to enhance stability (Hosoi *et al.*, J. Interferon Res. 8:375 (1988; Karpusas *et al.*, Cell Mol Life Sci 54:1203 (1998); Knight, J. Interferon Res. 2:421 (1982); Runkel *et al.*, Pharm Res 15:641 (1998); Lin, Dev. Biol. Stand. 96:97 (1998)). Interferon-γ contains two N-linked oligosaccharide chains at positions 25 and 97, both important for the efficient formation of the bioactive recombinant protein, and having an influence on the pharmacokinetic properties of the protein (Sareneva *et al.*, Eur. J. Biochem 242:191 (1996); Sareneva *et al.*, Biochem J. 303:831 (1994); Sareneva *et al.*, J. Interferon Res. 13:267 (1993)). Mixed O-linked and N-linked glycosylation also occurs, for example in human erythropoietin, N-linked glycosylation occurs at asparagine residues located at positions 24, 38 and 83 while O-linked glycosylation occurs at a serine residue located at position 126 (Lai *et al.*, J. Biol. Chem. 261:3116 (1986); Broudy *et al.*, Arch. Biochem. Biophys. 265:329 (1988)).

[0066] Therapeutic proteins corresponding to a Therapeutic protein portion of an

albumin fusion protein of the invention, as well as analogs and variants thereof, may be modified so that glycosylation at one or more sites is altered as a result of manipulation(s) of their nucleic acid sequence, by the host cell in which they are expressed, or due to other conditions of their expression. For example, glycosylation isomers may be produced by abolishing or introducing glycosylation sites, *e.g.*, by substitution or deletion of amino acid residues, such as substitution of glutamine for asparagine, or unglycosylated recombinant proteins may be produced by expressing the proteins in host cells that will not glycosylate them, *e.g.* in *E. coli* or glycosylation-deficient yeast. These approaches are described in more detail below and are known in the art.

[0067] Therapeutic proteins that may be used, for example, in treating (e.g., ameliorating) or preventing diabetes and a condition associated with diabetes are known in the art (e.g., those disclosed in Table 1 and nucleic acid sequences encoding these proteins). Many of the sequences corresponding to these Therapeutic proteins are available in public databases such as Chemical Abstracts Services Databases (e.g., the CAS Registry), GenBank, and subscription provided databases such as GeneSeq (e.g., Derwent). Exemplary nucleotide sequences of Therapeutic proteins which encode a polynucleotide of the invention are disclosed in column 7, "SEQ ID NO:X," of Table 2. Sequences shown as SEQ ID NO:X may be a wild type polynucleotide sequence encoding a given Therapeutic protein, or in some instances the sequence may be a variant of the wild type polynucleotide sequence (e.g., a polynucleotide which encodes the wild type Therapeutic protein optimized, for example, for expression in a particular host; or a polynucleotide encoding a variant of the wild type Therapeutic protein (e.g., a site directed mutant; an allelic variant)). It is well within the ability of the skilled artisan to use the sequence shown as SEQ ID NO:X to derive the construct described in the same row. For example, if SEQ ID NO:X corresponds to a full length protein, but only a portion of that protein is used to generate the specific CID, it is within the skill of the art to rely on molecular biology techniques, such as PCR, to amplify the specific fragment and clone it into the appropriate vector.

[0068] Additional Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention include, but are not limited to, one or more of the Therapeutic proteins or peptides disclosed in the "Therapeutic Protein X" column of Table 1, or fragment or variable thereof.

[0069] Table 1 provides a non-exhaustive list of Therapeutic proteins that correspond to a Therapeutic protein portion of an albumin fusion protein of the invention, and thus, an albumin fusion protein encoded by a polynucleotide of the invention. The first column, "Therapeutic Protein X," discloses Therapeutic protein molecules that may be followed by parentheses containing scientific and brand names of proteins that comprise, or alternatively consist of, that Therapeutic protein molecule or a fragment or variant thereof. "Therapeutic protein X" as used herein may refer either to an individual Therapeutic protein molecule, or to the entire group of Therapeutic proteins associated with a given Therapeutic protein molecule disclosed in this column. The "Biological activity" column (column 2) describes Biological activities associated with the Therapeutic protein molecule (and fragments and variants of the Therapeutic protein). Column 3, "Exemplary Activity Assay," provides references that describe assays which may be used or routinely modified to test the therapeutic and/or biological activity of a Therapeutic Protein X or an albumin fusion protein comprising a Therapeutic protein X portion. Each of the references cited in the "Exemplary Activity Assay" column are herein incorporated by reference in their entireties, particularly with respect to the description of the respective activity assay described in the reference (see Methods section therein, for example) for assaying the corresponding biological activity set forth in the "Biological Activity" column of Table 1. The fourth column, "Preferred Indication Y," describes disease, disorders, and/or conditions that may be treated (e.g., ameliorated), prevented, or diagnosed, by Therapeutic protein X or an albumin fusion protein comprising a Therapeutic protein X portion. The fifth column, "Therapeutic Protein Z" provides an amino acid sequence associated with the Therapeutic protein molecule (and fragments and variants of the Therapeutic protein). The "Construct ID" column (column 6) provides a link to an exemplary albumin fusion construct disclosed in Table 2 which encodes an albumin fusion protein comprising the referenced Therapeutic Protein X portion.

TABLE 1.

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
Insulin (Human insulin; Insulin aspart; Insulin Glargine; Insulin lispro; Lys-B28 Pro-B29; lyspro; LY 275585; diarginylinsulin; Des-B26-B30-insulin-B25-amide; Insulin detemir; LABI; NOVOLIN; NOVORAPID; HUMULIN; NOVOMIX 30; VELOSULIN; NOVOLOG; LANTUS; ILETIN; HUMALOG; MACRULIN; EXUBRA; INSUMAN; ORALIN; ORALGEN; HUMAHALE; HUMAHALIN)	Stimulates glucose uptake and promotes glycogenesis and lipogenesis.	Insulin activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2250, 2255, 2276, 2278, 2656, 2668, 2669, 2671, 2821, 2822, 2832, 2877, 2878, 2882, 2885, 2891, 2897, 2930, 2931, 2942, 2986, 3025, 3133, 3134, 3197, 3198, 2726, 2727, 2784, 2789
Glucagon-Like-Peptide 1 (GLP1; Insulinotropin)	Stimulates the synthesis and release of insulin; enhances the sensitivity of adipose, muscle, and liver tissues towards insulin; stimulates glucose	GLP1 activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2448, 2455, 2456, 2457, 2803, 2804, 2900, 2904, 2945, 2964, 2982, 3070, 2802, 3027, 3028, 3045, 3046, 3069,

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
	uptake; slows the digestive process; suppresses appetite; blocks the secretion of glucagon.		To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		3071, 3072, 3085, 3086, 3087, 3140, 3309
Exendin-4 (AC-2993)	Stimulates the synthesis and release of insulin; enhances the sensitivity of adipose, muscle, and liver tissues towards insulin; stimulates glucose uptake; slows the digestive process; suppresses appetite; blocks the secretion of glucagon.	Exendin-4 activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2469 and 2470.
Resistin	Mediates insulin resistance in Type II diabetes; inhibits insulin-stimulated glucose uptake	Ability of resistin to influence type II diabetes can be determined using assays known in the art: Pontoglio et al., J Clin Invest 1998 May 15;101(10):2215-22.	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite;	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2295, 2296, 2297, 2300, and 2309.

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			Syndrome X.		
Leptin	Controls obesity through regulation of appetite, reduction of body weight, and lowering of insulin and glucose level.	In vivo modulation of food intake, reduction in body weight, and lowering of insulin and glucose levels in ob/ob mice, radioimmunoassay (RIA) and activation of the leptin receptor in a cell-based assay. Protein Expr Purif 1998 Dec;14(3):335-42	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); a Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Immunological Disorders; Immunosuppression.	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2146, 2184, 2186, and 2187.
HLDOU18 (Bone Morphogenic Protein 9 (BMP9); Growth differentiation factor-2 precursor (GDF-2 precursor))	Activates L6/GSK3 kinase assay.	Assays for activation of GSK3 kinase activity are well known in the art. For example, Biol. Chem. 379(8-9): (1998) 1101-1110.; Biochem J. 1993 Nov 15;296 (Pt 1):15-9.	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	22328, 2340, 22350, 2351, 22359, 2362, 22367, 2369, 22370, 2473, 2623, 2624, 2625, 2631, 2632, 2633.
IL-22 (IL22, interleukin-22; IL17D, IL27)	Stimulates glucose uptake in skeletal muscle cells;	IL-22 activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin	*See TABLE 2 for the Therapeutic protein description under the	2901, 2903

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
	increases skeletal muscle insulin sensitivity.	Biol Chem 1999 Oct 22; 274(43):30864-30873).	resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	corresponding Construct ID number	
RegIV (Colon Specific Gene; Colon Specific Protein)	Stimulates glucose uptake; increases insulin sensitivity.	RegIV activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2910.
Interferon alfa (Interferon alfa-2b; recombinant; Interferon alfa-n1; Interferon alfa-n3; Peginterferon alpha-2b; Ribavirin and interferon alfa-2b;	Stimulates glucose uptake; increases insulin sensitivity.	Interferon activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia, Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2249, 2343, 2366, 2381, 2382, 2410, and 3165.

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
Interferon alfacon-1; interferon consensus; YM 643; CIFN; interferon -alpha consensus; recombinant methionyl consensus interferon; recombinant consensus interferon; CGP 35269; RO 253036; RO 258310; INTRON A; PEG-INTRON; OIF; OMNIFERON; PEG-OMNIFERON; VELDONA; PEG-REBETRON; ROFERON A; WELLFERON; ALFERON N/LDO; REBETRON; ALTEMOL; VIRAFERONPEG; PEGASYS; VIRAFERON; VIRAFON; AMPLIGEN; INFERGEN; INFAREX; ORAGEN)			With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
HCE1P80	Stimulates glucose uptake; increases insulin sensitivity.	HCE1P80 activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2908, 3049, 3050, 3051, 3052.

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			(NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
HDRMI82	Stimulates glucose uptake; increases insulin sensitivity.	HDRMI82 activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	2909.
PYY (Peptide YY) including PYY_{3-36} (amino acid residues 31-64 of full length PYY, amino acid residues 3-36 of mature PYY)	Decreases appetite; increases satiety; decreases food intake.	Appetite and food intake can be can be measured by methods known in the art (Batterham et al. Nature 2002; 418:650654); Activity may also be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Most preferred: Treatment of Obesity; treatment of Diabetes; suppression of body weight gain; suppression of appetite. Also Preferred: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	3108, 3109, 3281, 3117, 3118, 3282.

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X. Other indications for antibodies, antagonists: treatment of weight loss; treatment of AIDS wasting; appetite stimulant; treatment of cachexia.		
HCBOG68 (enteric adipokine; Fat SID; proline rich acidic protein)	Controls proliferation/ differentiation or metabolism/ physiology/patholo gy/ of adipocytes and adipose tissue in response to dietary conditions.	Activation of cAMP-mediated transcription in adipocytes can be assayed using methods known in the art (Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998)); Activity may also be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Treatment of Obesity; treatment of Diabetes; suppression of body weight gain; suppression of appetite. Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X. Other indications for antibodies and/ or antagonists include treatment of weight loss; treatment of AIDS wasting; appetite stimulant; treatment of cachexia.	*See TABLE 2 for the Therapeutic protein description under the corresponding Construct ID number	3106, 3270
F-992	Vasopressin	Activity may be assayed in	Hyperglycemia; Diabetes; Diabetes	Vasopressin (Genbank	

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
(Ferring Pharmaceuticals)	agonist	vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	Accession AAB86629) and/or fragments or variants thereof including but not limited to [D-Phe^{2}-Thi^{3}-alpha-Me-Abu^{4}-Hyp^{7}-D-Arg^{8}]-dC^{1}-vasopressin.	
INGAP peptide (GMP Companies)	Stimulates the synthesis and release of insulin; enhances the sensitivity of adipose, muscle, and liver tissues towards insulin; stimulates glucose uptake; slows the digestive process; suppresses appetite; blocks the secretion of glucagons; involves islet neogenesis associated protein	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	SEQ ID NO:840 (See Genbank Accession No. U41737) and/or fragments or variants thereof.	
Chrysalin (Chrysalis Biotechnology)	Thrombin mimetic; chemotactic for neutrophils;	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem	Most preferred indications include: Diabetic foot ulcer; bone fractures; chronic wound healing; heart angiogenesis; cartilage	SEQ ID NO:841 (508-530 of mature prothrombin); or	

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
	enhance collagen accumulation in wounds; enhance revascularization of wounds; accelerate healing of incisional and open wounds in normal animals and in animals with impaired healing	1999 Oct 22; 274(43):30864-30873).	repair and spine surgery (spinal fusion repair); and a condition associated with diabetes including but not limited to obesity, heart disease, hyperglycemia, infections, and as otherwise described herein. Also preferred are: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	SEQ ID NO:842 (508-530 of preprothrombin, see Genbank Accession No. P00734); and/or fragments or variants thereof.	
NBI-6024 (Neurocrine Biosciences)	Therapeutic vaccine to elicit a potentially protective immune response to slow islet cell destruction	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite;	SEQ ID NO:843 and/or fragments or variants thereof	

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			Syndrome X.		
SPM-933 (Schwarz Pharma AG and Creative Peptides)	C-peptide analog	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	SEQ ID NO:844 (see Genbank Accession No. P01308) and/or fragments or variants thereof.	
Octreotide; SMS 995, Sandostatin LAR (Novartis)	Growth hormone antagonist (somatostatin analog)	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Proliferative diabetic retinopathy; prevention of obesity; metastatic carcinoid syndrome and acromegaly; control diarrhea due to vasoactive intestinal peptide-secreting tumours; prevention of variceal bleeds; psoriasis; viral infection; Alzheimer's disease and migraine. Also preferred include: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited	SEQ ID NO:845 and/or fragments or variants thereof including but not limited to [R-(R*,R*)]-D-Phe-L-Cys-L-Phe-D-Trp-L-Lys-L-Thr-N-[2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2-7)-disulfide.	

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy		
Pexiganan Acetate (CAS-172820-23-4)	Anti-infective; Disrupts bacterial membranes.	Pexiganan acetate activity can be assessed using in vitro antibacterial assays known in the art. (Zasloff et al., Antimicrobial Agents and Chemotherapy 1999, 43:782-788); Activity may be also assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873)..	Most preferred include: Diabetic foot ulcer; wound healing; diabetic foot ulcer infections; bacterial infection; impetigo; burns; and a condition associated with diabetes including but not limited to obesity, heart disease, hyperglycemia, infections, and as otherwise described herein. Also preferred include: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression	Lysinamide (SEQ ID NO:846) acetate and/or fragments or variants thereof.	

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			of Appetite; Syndrome X.		
Pramlintide (Amylin) (CAS-151126-32-8)	Amylin analog; improves glycemic control; reduces postprandial blood glucose peaks; flattens glucose peaks and troughs observed in diabetic patients; Slows gastric emptying; decreases food intake.	Appetite and food intake can be can be measured by methods known in the art (Batterham et al. Nature 2002; 418:650654); Activity may be also assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Treatment of Obesity; treatment of Diabetes; suppression of body weight gain; suppression of appetite; treatment of endocrine disorders; Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X. Other indications for antibodies, antagonists: treatment of weight loss; treatment of AIDS wasting; appetite stimulant; treatment of cachexia	SEQ ID NC:847, with a C-termnal L-tyrosinamide cyclic (2-7)-disulfide and/or fragments or variants thereof.	
HP-228 (LION Biosciences)	Cytokine release modulator; melanocortin modulator; lowers plasma insulin and glucose levels	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Diabetes mellitus; obesity; inflammation; pain; chemotherapy-induced emesis; toxicity; and a condition associated with diabetes including but not limited to obesity, heart disease, hyperglycemia, infections, and as otherwise described herein. Also preferred include: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency;	SEQ ID NO:848 and/or fragments or variants thereof including but not limited to N-acetyl-L-norleucyl-L-Gln-L-His-D-Phe-L-Arg-D-Trp-Glycinamide.	

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
Neurulin (Cortecs International Ltd)		Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873)..	Most preferred: Diabetic Neuropathy; and a condition associated with diabetes including but not limited to obesity, heart disease, hyperglycemia, infections, and as otherwise described herein. Also preferred: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression		

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			of Appetite; Syndrome X.		
AC-253 (Amylin Pharmaceuticals)	GLP-1 agonist; appetite suppressant; hypoglycemic agent; amylin antagonist	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Most preferred: Type II NIDDM; obesity; hypertension; and a condition associated with diabetes including but not limited to obesity, heart disease, hyperglycemia, infections, and as otherwise described herein. Also preferred: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
ALT-300 (Alteon)	Glucagon antagonist; lowers plasma glucose levels	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Most preferred: Type I IDDM and Type II NIDDM; acidosis; and a condition associated with diabetes including but not limited to obesity, heart disease, hyperglycemia, infections, and as otherwise described herein. Also preferred: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin		

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
ANERVAX.DB (Corixa Corp)	Peptide vaccine; delay and suppress the development of Type I IDDM	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
AZM-140 (Alizyme)	Amylase inhibitor; hypoglycemic agent	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22;	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency;		

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
		274(43):30864-30873).	Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
Interferon beta (Interferon beta-1a; Interferon beta 1b; Interferon-beta-serine; SH 579; ZK 157046; BCDF; beta-2 IF; Interferon-beta-2; rhIL-6; SJ0031; DL 8234; FERON; IFNbeta; BETASERON; AVONEX; REBIF; BETAFERON; SIGOSIX)	Modulates MHC antigen expression, NK cell activity and IFNg production and IL12 production in monocytes.	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	See Table 2, SEQ ID NO:Z for particular construct.	1778, 1779, 2011, 2013, 2053, 2054, 2492, 2580, 2795, 2796, 2797
TR6 (DcR3; Decoy Receptor 3; FASTR)	Inhibits Fas Ligand and AIM-2 (TL5, LIGHT) mediated apoptosis.	Cellular apoptosis can be measured by annexin staining, TUNEL staining, measurement of caspase levels. Inhibition of cell growth can also be directly measured, for example by	Renal failure; insulin dependent diabetes mellitus; rheumatoid arthritis; inflammatory bowel disease; autoimmune disease; toxic epidermal necrolysis; multiple sclerosis. Also preferred: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type	See Table 2, SEQ ID NO:Z for particular construct.	1520, 1537, 1545, 1546, 1568, 1570, 1622, 1623, 1645, 1700, 1702, 1703, 1704, 1891,

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
		ALOMAR Blue staining. Assay refs: cytotoxicity assay on human fibrosarcoma (Epsevik and Nissen-Meyer, 1986, J. Immunol. methods); Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		1892, 1912, and 1913.
TNFR2 (p75) (ENBREL)	Binds both TNFa and TNFb; mediates T-cell proliferation by TNF; reduces signs and structural damage in patients with moderately to severly active rheumatoid arthritis (RA).	T-cell proliferation can be measured using assays known in the art. For example, "Lymphocytes: a practical approach" edited by: SL Rowland, AJ McMichael – ch. 6, pages 138-160 Oxford University Press (2000); and "Current Protocols on CD-ROM" section 3.12 Proliferation Assays for T-cell Function John Wiley & Soncs, Inc. (1999); Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	See Table 2, SEQ ID NO:Z for particular construct.	1777 and 1784.
ACE2 inhibitor (DX512)	Inhibits production of angiotensin II which induces	Inhibition of angiotensin can be determined using assays known in the art. For	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin	See Table 2, SEQ ID NO:Z for particular construct.	1989, 2000, 2001, and 2002.

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
	aldosterone production, arteriolar smooth muscle vasoconstriction, and proliferation of cardiac fibroblasts, Induces angiogenesis; an enzyme that converts angiotensin I to angiotensin1-9; also cleaves des-Arg, bradykinin and neurotensin.	example, in vitro using a proliferation assay with rat cardiac fibroblasts as described in Naunyn Schmiedebergs Arch Pharmacol 1999 May;359(5):394-9; Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Proteinuria; Renal disorders, congestive heart failure.		
Interferon Hybrids, specifically preferred: IFNalpha A/D hybrid (BgIII version) IFNalpha A/D hybrid (PvuII version) IFNalpha A/F hybrid IFNalpha A/B hybrid IFNbeta 1/alpha D hybrid (IFNbeta-1/alpha-1 hybrid) IFNalpha/beta hybrid	Confers a range of cellular responses including antiviral, antiproliferative, antitumor and immunomodulatory activities; stimulate production of two enzymes: a protein kinase and an oligoadenylate synthetase. Also, modulates MHC antigen expression, NK cell activity and IFNg production and IL12 production in monocytes.	Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.	See Table 2, SEQ ID NO:Z for particular construct.	2875, 2872, 2876, 2874, 2873.

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
HWHGZ51 (CD59; Metastasis-associated GPI-adhered protein homolog)	Stimulates an immune response and induces inflammation by inducing mononuclear cell, eosinophil and PMN infiltration; Inhibits growth of breast cancer, ovarian cancer, leukemia, and melanoma; Overexpressed in colon, lung, breast and rectal tumors; Regulates glucose and/or FFA update by adipocytes and skeletal muscle; Induces redifferentiation of chondrocytes	The ability to affect chondrocyte differentiation can be measured using methods known in the art, such as described in Bone (1995) Sep; 17(3):279-86; Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia, Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Kidney disorders; Hyperinsulinemia; Hypoinsulinemia	See Table 2, SEQ ID NO:Z for particular construct.	2407, 2408
C17 (cytokine-like protein C17)	Inhibits glucose and/or FFA uptake by adipocytes; Induces proliferation of kidney mesangial cells; Regulation of cytokine production and antigen presentation	Proliferation of kidney mesangial cells can be assayed using techniques described in J. Investig. Med. (1998) Aug; 46(6):297-302; Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Kidney diseases and disorders; Shonlein-Henoch purpura, Berger disease, celiac disease, dermatitis herpetiformis, Chron disease; Hyperglycemia, Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited	See Table 2, SEQ ID NO:Z for particular construct.	2489, 2490

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Kidney disorders; Hyperinsulinemia; Hypoinsulinemia		
Somatostatin (Octreotide; octreotide acetate; Sandostating LAR®)	Inhibits growth hormone, glucagons and insulin; Suppresses LF response to GnRH; Decreases splanchnic blood flow; Inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.	Inhibition of growth hormone release in humans by somatostatin can be measured as described in J. Clin. Endocrinol. Metab. (1973) Oct; 37(4):632-4. Inhibition of insulin secretion by somatostatin can be measured as described in the Lancet (1973) Dec. 8; 2(7841):1299-1301; Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia, Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Kidney disorders	See Table 2, SEQ ID NO:Z for particular construct.	2798, 2825, 2830, 2831, 2902
HDALV07 (adiponectin; gelatin-binding 28k protein precurson; adipose most abundant gene transcript; APM-1; GBP28; ACRP30; ADIPOQ)	Modulates insulin action	HDALV07 activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia, Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers;	See Table 2, SEQ ID NO:Z for particular construct.	3053, 3055, 3056

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Hyperglycemia; Familial combined hyperlipidemia; Metabolic syndrome		
C Peptide	An insulin precursor involved in insulin regulation	C-peptide concentrations can be measured using assays well known in the art, such as the one described in PNAS (1970) Sep; 67(1):148-55; Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Hyperglycemia, Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X; Hyperglycemia; Familial combined hyperlipidemia; Metabolic syndrome	See Table 2, SEQ ID NO:Z for particular construct.	3088, 3149
WNT10b	Inhibits adipogenesis.	WNT10b activity can be measured using adipogenesis inhibition assays (Ross et al., Science 2000; 289(5481):950-953; Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Most preferred: Treatment of Obesity; suppression of body weight gain; suppression of appetite. Other indications: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM).	See Table 2, SEQ ID NO:Z for particular construct.	3141

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			Also preferred: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		
CART (Cocaine- and Amphetamine-Regulated Transcript)	Inhibits food intact and fat storage; promotes lipid oxidation.	Appetite and food intake can be can be measured by methods known in the art (Batterham et al. Nature 2002; 418:650654); Activity may be assayed in vitro using a [3-H]-glucose uptake assay. (J Biol Chem 1999 Oct 22; 274(43):30864-30873).	Most preferred: Treatment of Obesity; suppression of body weight gain; suppression of appetite. Other indications: Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Late-stage diabetic complications of Type I IDDM (e.g., nephropathy, neuropathy, and retinopathy; Metabolic Disorders; Immune	See Table 2, SEQ ID NO:Z for particular construct.	3232

Therapeutic Protein:X	Biological Activity	Exemplary Activity Assay	Preferred Indication:Y	Therapeutic Protein:Z	Construct ID
			Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X.		

Table 2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
1	1520	pC4:HSA/TR6.V30-H300	Amino acids V30 to H300 of TR6 (fragment shown as V1 to H271 of SEQ ID NO:139) fused downstream of HSA.	pC4	70	1	139	208	209	HSA
2	1537	pYPG:HSA.TR6coV30-E294	Amino acids V30 to E294 of TR6 (fragment shown as V1 to E265 of SEQ ID NO:140) fused downstream of HSA. DNA encoding TR6 has been codon optimized.	pYPGaf	71	2	140	210	211	HSA
3	1545	pYPG:HSA.TR6coV30-L288	Amino acids V30 to L288 of TR6 (fragment shown as V1 to L259 of SEQ ID NO:141) fused downstream of HSA. DNA encoding TR6 has been codon optimized.	pYPGaf	72	3	141	212	213	HSA
4	1546	pYPG:HSA.TR6coV30-R284	Amino acids V30 to R284 of TR6 (fragment shown as V1 to R255 of SEQ ID NO:142) fused downstream of HSA. DNA encoding TR6 has been codon optimized.	pYPGaf	73	4	142	214	215	HSA
5	1568	pSAC35:HSA-yTR6	TR6 fused downstream of HSA. DNA encoding TR6 has been codon optimized.	pSAC35	74	5	143	216	217	HSA/kex2
6	1570	pSAC35:TR6-HSA	Mature TR6 fused downstream of the HSA/kex2 leader and upstream of the mature HSA.	pSAC35	75	6	144	218	219	HSA/kex2
7	1622	pC4:synTR6.M1-H300.HSA	Synthetic TR6 fused upstream of mature HSA, with 2 extra amino acids between the TR6 and HSA portions.	pC4	76	7	145	220	221	Native TR6
8	1623	pC4:HSA.synTR6.V3	Synthetic mature TR6 fused	pC4	77	8	146	222	223	HSA

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
		0-H300	downstream of FL HSA. Last amino acid HSA sequence is missing at BSU36I site.							
9	1645	pSAC35:yTR6(N173Q).HSA	Mutant mature TR6 cloned upstream of mature HSA and downstream of the HSA/kex2 leader sequence.	pSAC35	78	9	147	224	225	HSA/kex2
10	1700	pSAC35:HSA-yTR6(N173Q)	Mutant TR6 fused downstream of mature HSA with HSA/kex2 leader sequence.	pSAC35	79	10	148	226	227	HSA/kex2
11	1702	pYPG:HSA.ek.TR6coV30-L288	Amino acids V30 to L288 of TR6 (fragment shown as V1 to L259 of SEQ ID NO:149) fused downstream of FL HSA with an enterokinase site in between. DNA encoding TR6 has been codon optimized.	pYPGaf	80	11	149	228	229	HSA
12	1703	pYPG:HSA.ek.TR6coV30-R284	Amino acids V30 to R284 of TR6 (fragment shown as V1 to R255 of SEQ ID NO:150) fused downstream of HSA with an enterokinase site in between. DNA encoding TR6 has been codon optimized.	pYPGaf	81	12	150	230	231	HSA
13	1704	pYPG:HSA.TR6.V30-E294	Amino acids V30 to E294 of TR6 fused downstream of HSA. Two additional amino acids (Leu, Glu) are in between HSA and TR6.	pYPGaf	82	13	151	232	233	HSA
14	1777	pSAC35:TNFR2.L23-D257.HSA	Mature TNFR2 fused downstream of the HSA/kex2 signal and upstream of mature HSA.	pSAC35	83	14	152	234	235	HSA/kex2
15	1778	pSAC35:IFNβ.M22-N187:HSA	Residues M22-N187 of full-length IFNb (shown as M1 to N166 of SEQ ID NO:153) fused upstream of mature	pSAC35	84	15	153	236	237	HSA/kex2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			HSA and downstream of HSA/kex2 leader sequence.							
16	1779	pSAC35:HSA:IFNβ. M22-N187	Residues M22-N187 of full-length IFNb (shown as M1 to N166 of SEQ ID NO:154) fused downstream of HSA with HSA/kex2 leader sequence.	pSAC35	85	16	154			HSA/kex2
17	1784	pSAC35:HSA.TNFR 2.L23-D257	Mature TNFR2 fused downstream of FL HSA.	pSAC35	86	17	155	238	239	HSA
18	1891	pEE12:HSA.sTR6	Soluble mature TR6 fused downstream of HSA.	pEE12.1	87	18	156	240	241	HSA
19	1892	pEE12:sTR6.HSA	Synthetic full length TR6 fused upstream of mature HSA.	pEE12.1	88	19	157	242	243	TR6
20	1912	pC4:sTR6.HSA	Synthetic full length TR6 fused upstream of mature HSA.	pC4	89	20	158	244	245	Native TR6 leader
21	1913	pC4:HSA.synTR6.V30-H300 (seamless)	Amino acids V30 to H300 of synthetic TR6 (shown as V1 to H271 of SEQ ID NO:159) fused downstream of full-length HSA.	pC4	90	21	159	246	247	HSA
22	1989	pSAC35:activeAC2inhibitor:HSA	Active inhibitor of ACE2 (DX512) fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	91	22	160	248	249	HSA/kex2
23	2000	pSAC35:HSA:activeAC2inhibitor	Active inhibitor of ACE2 (DX512) fused downstream of HSA.	pSAC35	92	23	161	250	251	HSA
24	2001	pSAC35:inactiveAC2inhibitor:HSA	Inactive inhibitor of ACE2 (DX510) fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	93	24	162	252	253	HSA/kex2
25	2002	pSAC35:HSA.inactiveAC2inhibitor	Inactive inhibitor of ACE2 (DX510) fused downstream of HSA.	pSAC35	94	25	163	254	255	HSA
26	2011	pC4:IFNb-HSA	Full length IFNb fused upstream of	pC4	95	26	164	256	257	Native

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			mature HSA.							IFNb leader
27	2013	pC4:HSA-IFNb.M22-N187	Amino acids M22 to N187 of IFNb (fragment shown as amino acids M1 to N166 of SEQ ID NO:165) fused downstream of HSA.	pC4	96	27	165			HSA
28	2053	pEE12:IFNb-HSA also named pEE12.1:IFNβ-HSA	Full length IFNb fused upstream of mature HSA.	pEE12.1	97	28	166			Native IFNb leader
29	2054	pEE12:HSA-IFNb	Mature IFNb fused downstream of HSA.	pEE12.1	98	29	167			HSA
30	2146	pC4:Leptin.HSA	Full length Leptin fused upstream of mature HSA.	pC4	99	30	168	258	259	Native leptin
31	2184	pC4:HSA.Leptin.V22-C166	Amino acids V22 to C167 of Leptin fused downstream of HSA.	pC4	100	31	169	260	261	HSA
32	2186	pSAC35:Leptin.V22-C166.HSA	Amino acids V22 to C167 of Leptin fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	101	32	170	262	263	HSA/kex2
33	2187	pSAC35:HSA.Leptin.V22-C166	Amino acids V22 to C167 of Leptin fused downstream of HSA with HSA/kex2 leader sequence.	pSAC35	102	33	171	264	265	HSA/kex2
34	2249	pSAC35:IFNa2-HSA also named: pSAC23:IFNα2-HSA	Mature IFNa2 fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	103	34	172	266	267	HSA/kex2
35	2250	pSAC35:HSA.INSULIN(GYG)	Mature Insulin wherein the C-peptide is replaced by the C-domain of IGF-1 fused downstream of HSA. DNA encoding Insulin was codon	pSAC35	104	35	173	268	269	HSA

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
		also named: pSAC35.HSA.INSULING(GYG).F1-N62	optimized.							
36	2255	pSAC35:INSULIN(GYG).HSA also named pSAC35.INSULING(GYG).F1-N62.HSA	Mature Insulin wherein the C-peptide is replaced by the C-domain of IGF-1 fused upstream of mature HSA and downstream of HSA/kex2 leader. DNA encoding Insulin was codon optimized.	pSAC35	105	36	174	271	272	HSA/kex2
37	2276	pSAC35:HSA.INSULIN(GGG) also named: pSAC35.HSA.INSULING(GGG).F1-N58	Mature Insulin wherein the C-peptide is replaced by a synthetic linker fused downstream of HSA. DNA encoding Insulin was codon optimized.	pSAC35	106	37	175	273	274	HSA
38	2278	pSAC35:insulin(GGG).HSA	Mature Insulin wherein the C-peptide is replaced by a synthetic linker fused downstream of HSA/kex2 leader and upstream of mature HSA. DNA encoding Insulin was codon optimized.	pSAC35	107	38	176	275	276	HSA/kex2
39	2295	pSAC35:humanresistin.K19-P108:HSA	Amino acids K19 to P108 of Resistin fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	108	39	177	277	278	HSA/kex2
40	2296	pSAC35:HSA:humanresistin.K19-P108	Amino acids K19 to P108 of Resistin fused downstream of HSA.	pSAC35	109	40	178	279	280	HSA
41	2297	pSAC35:humanresistin.K19-P108.stop:HSA	Amino acids K19 to P108 of Resistin fused upstream of mature HSA and downstream of HSA/kex2 leader	pSAC35	110	41	179	281	282	HSA/kex2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			sequence. Includes two stops at 3' end for termination of translation before the HSA.							
42	2300	pC4:humanresistin.M1-P108:HSA	Amino acids M1 to P108 of Resistin fused upstream of mature HSA.	pC4	111	42	180	283	284	Native resistin
43	2309	pEE12.1:humanresistin.M1-P108:HSA	Amino acids M1 to P108 of Resistin fused upstream of mature HSA.	pEE12.1	112	43	181	285		Native resistin
44	2328	pC4:HLDOU18.K23-R429.HSA	Amino acids K23 to R429 of HLDOU18 fused upstream of mature HSA and downstream of native HSA leader sequence.	pC4	113	44	182	286	287	HSA
45	2340	pC4:HSA.HLDOU18.K23-R429	Amino acids K23 to R429 of HLDOU18 fused downstream of HSA.	pC4	114	45	183	288	289	HSA
46	2343	pSAC35.INV-IFNA2.HSA	Mature Interferon alpha2 fused upstream of mature HSA and downstream of invertase signal peptide.	pSAC35	115	46	184	290	291	invertase
47	2350	pC4:MPIFsp.HLDOU18(S320-R429).HSA	Amino acids S320 to R429 of HLDOU18 fused upstream of mature HSA and downstream of MPIF leader sequence.	pC4	116	47	185	292	293	MPIF
48	2351	pC4:HSA.HLDOU18(S320-R429)	Amino acids S320 to R429 of HLDOU18 fused downstream of HSA.	pC4	117	48	186	294	295	HSA
49	2359	pEE12:HLDOU18.K23-R429.HSA	Amino acids K23 to R429 of HLDOU18 fused upstream of mature HSA and downstream of native HSA leader sequence.	pEE12.1	118	49	187			HSA
50	2362	pEE12:HSA.HLDOU18.K23-R429	Amino acids K23 to R429 of HLDOU18 fused downstream of	pEE12.1	119	50	188			HSA

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			HSA.							
51	2366	pSAC35.MAF-IFNa2.HSA	Mature IFNa2 fused upstream of mature HSA and downstream of yeast mating factor alpha leader sequence.	PSAC35	120	51	189	296	297	MFα-1
52	2367	pEE12.MPIFsp.HLDOU18.S320-R429.HSA	Amino acids S320 to R429 of HLDOU18 fused upstream of mature HSA and downstream of MPIF leader sequence.	pEE12.1	121	52	190	298	299	MPIF
53	2369	pC4:HLDOU18.HSA	Amino acids M1 to R429 of HLDOU18 fused upstream of mature HSA.	pC4	122	53	191	300	301	Native HLDOU18
54	2370	pEE12:HLDOU18.HSA	Amino acids M1 to R429 of HLDOU18 fused upstream of mature HSA.	pEE12.1	123	54	192			Native HLDOU18
55	2381	pC4:HSA-IFNa2(C17-E181)	Amino acids C17 to E181 of IFNa2 (fragment shown as amino acids C1 to E165 of SEQ ID NO:193) fused downstream of HSA.	pC4	124	55	193	302	303	HSA
56	2382	pC4:IFNa2-HSA	IFNa2 fused upstream of mature HSA.	pC4	125	56	194	304	305	Native IFNα2 leader
57	2407	pC4:HWHGZ51.M1-N323.HSA	Amino acids M1 to N323 of HWHGZ51 fused upstream of mature HSA.	pC4	126	57	195	306	307	Native HWHGZ51
58	2408	pEE12.1:HWHGZ51.M1-N323.HSA	Amino acids M1 to N323 of HWHGZ51 fused upstream of mature HSA.	pEE12.1	127	58	196	308	309	Native HWHGZ51
59	2410	pSAC35INV:IFNa-HSA	Mature IFNa2 fused downstream of the invertase signal peptide and upstream of mature HSA.	pSAC35	128	59	197	310	311	invertase
60	2448	pSAC35:GLP-1(7-	Amino acids H98 to R127 of	pSAC35	129	60	198	312	313	HSA/kex2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
		36).HSA	preproglucagon (SEQ ID NO:198) (hereinafter this specific domain will be referred to as "GLP-1(7-36)") is fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.							
61	2455	pSAC35:HSA.GLP-1(7-36)	GLP-1(7-36) is fused downstream of mature HSA and HSA/kex2 leader sequence.	pSAC35	130	61	199	314	315	HSA/kex2
62	2456	pSAC35:GLP-1(7-36(A8G)).HSA	Amino acids H98 to R127 of Preproglucagon (SEQ ID NO:200)(also referred to as "GLP-1(7-36)") is mutated at amino acid 99 of SEQ ID NO:200 to replace the alanine with a glycine. This particular GLP-1 mutant will be hereinafter referred to as "GLP-1(7-36(A8G))" and corresponds to the sequence shown in SEQ ID NO:698. GLP-1(7-36(A8G)) is fused upstream of mature HSA and downstream of HSA/kex2 leader sequence.	pSAC35	131	62	200	316	317	HSA/kex2
63	2457	pSAC35:HSA.GLP-1(7-36(A8G))	GLP-1(7-36(A8G)) (SEQ ID NO:698) is fused downstream of mature HSA and HSA/kex2 leader sequence.	pSAC35	132	63	201	318	319	HSA/kex2
64	2469	pSAC35:HSA.exendin.H48-S86	Amino acids H48 to S86 of Extendin fused downstream of full length HSA.	pSAC35	133	64	202			HSA
65	2470	pSAC35:Exendin.H48-S86.HSA	Amino acids H48 to S86 of Extendin fused upstream of mature HSA and downstream of HSA/kex2 leader	pSAC35	134	65	203			HSA/kex2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			sequence.							
66	2473	pC4.HLDOU18:HSA :S320-R429	M1-R319 of HLDOU18 (containing the furin site RRKR) followed by residues 'LE' followed by mature HSA followed by 'LE' and amino acids S320 through R429 of HLDOU18 (fragment shown as SEQ ID NO:204).	pC4	135	66	204	320	321	Native HLDOU18
67	2489	pSAC35:HSA.C17.A 20-R136	Amino acids A20 to R136 of C17 fused downstream of mature HSA with HSA/kex2 leader sequence.	pSAC35	136	67	205	322	323	HSA/kex2
68	2490	pSAC35:C17.A20-R136.HSA	Amino acids A20 to R136 of C17 fused downstream of the HSA/kex2 leader and upstream of mature HSA.	pSAC35	137	68	206	324	325	HSA/kex2
69	2492	pC4.IFNb(deltaM22). HSA	Mutant full length INFbeta fused upstream of mature HSA. First residue of native, mature IFNbeta (M22) has been deleted.	pC4	138	69	207			Native IFNβ leader
70	2580	pC4.IFNb(deltaM22, C38S).HSA	IFNb fused upstream of mature HSA. The IFNb used in this fusion lacks the first residue of the mature form of IFNb, which corresponds to M22 of SEQ ID NO:632. Also amino acid 38 of SEQ ID NO:632 has been mutated from Cys to Ser.	pC4	555	480	632			Native IFNβ
71	2623	pC4:(AGVSG,14-18)HSA.HLDOU18. K23-R429	A modified HSA A14 leader followed by mature HSA and amino acids K23 through R429 of HLDOU18.	pC4	556	481	633			Modified HSA (A14) leader
72	2624	pC4:(SGVSG,14-18)HSA.HLDOU18. K23-R429	Modified HSA S14 leader followed by mature HSA and amino acids K23 to R429 of HLDOU18.	pC4	557	482	634			Modified HSA (S14) leader

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
73	2625	pC4:(GGVSG,14-18)HSA.HLDOU18.K23-R429	A modified HSA G14 leader sequence followed by mature HSA and amino acids K23 through R429 of HLDOU18.	pC4	558	483	635			Modified HSA (G14) leader
74	2631	pEE12.1:(AGVSG,14-18)HSA.HLDOU18.K23-R429	A modified HSA A14 leader sequence followed by mature HSA and amino acids K23 through R429 of HLDOU18.	pEE12.1	559	484	636			Modified HSA (A14) leader
75	2632	pEE12.1:(SGVSG,14-18)HSA.HLDOU18.K23-R429	Modified HSA S14 leader followed by mature HSA and amino acids K23 to R429 of HLDOU18.	pEE12.1	560	485	637			Modified HSA (S14) leader
76	2633	pEE12.1:(GGVSG,14-18)HSA.HLDOU18.K23-R429	A modified HSA G14 leader sequence followed by mature HSA and amino acids K23 through R429 of HLDOU18.	pEE12.1	561	486	638			Modified HSA (G14) leader
77	2656	pSac35:Insulin(KR.GGG.KR).HSA	Synthetic gene coding for a single-chain insulin with HSA at C-terminus. Contains a modified loop for processing resulting in correctly disulfide bonded insulin coupled to HSA.	pScCHSA	562	487	639	707	708	HSA/kex2
78	2668	pSac35:HSA.Insulin(KR.GGG.KR)	Synthetic gene coding for insulin with FL HSA at N-terminus. Contains a modified loop for processing resulting in correctly disulfide bonded insulin coupled to HSA.	pScNHSA	563	488	640	709	710	HSA
79	2669	pSac35:Insulin(GGG.KK).HSA	Synthetic gene coding for a single-chain insulin with HSA at C-terminus. Contains a modified loop.	pScCHSA	564	489	641	711	712	HSA/kex2
80	2671	pSac35:HSA.Insulin(	Synthetic gene coding for a single-	pScNHSA	565	490	642	713	714	HSA

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
		GGG.KK)	chain insulin with HSA at N-terminus. Contains a modified loop for greater stability.							
81	2726	pSac35.INV.GYGinsulin.HSA	Synthetic gene coding for a single-chain insulin with HSA at C-terminus. The signal peptide of invertase is used for this construct.	pSAC35	566	491	643	715	716	Invertase
82	2727	pSac35.INV.GYGinsulin(delF1).HSA	Synthetic gene coding for a single-chain insulin with HSA at C-terminus. Construct uses the invertase signal peptide and is lacking the first amino acid (F) of mature human insulin.	pSAC35	567	492	644	717	718	invertase
83	2784	pSAC35:Insulin(GYG)-HSA codon optimized	Synthetic gene coding for a single-chain insulin with HSA at C-terminus.	pSAC35	568	493	645	719	720	invertase
84	2789	pSAC35:Insulin(GGG).HSA (codon optimized)	Synthetic gene coding for a single-chain insulin with HSA at C-terminus.	pSAC35	569	494	646	721	722	invertase
85	2795	pC4:HSA(A14)-IFNb.M22-N187	The mature form of IFNb is fused to the C-terminus of HSA, which contains an modified signal peptide, designed to improve processing and homogeneity.	pC4	570	495	647			Modified HSA (A14)
86	2796	pC4:HSA(S14)-IFNb.M22-N187	The mature form of IFNb is fused to the C-terminus of HSA, which contains a modified signal peptide, designed to improve processing and homogeneity.	pC4	571	496	648			Modified HSA (S14)
87	2797	pC4:HSA(G14)-IFNb.M22-N187	The mature form of IFNb is fused to the C-terminus of HSA, which contains an modified signal peptide.	pC4	572	497	649			Modified HSA (G14)

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
88	2798	pSAC35:Somatostatin(S14).HSA	A 14 amino acid peptide of Somatostatin fused downstream of HSA/kex2 leader and upstream of mature HSA.	pScCHSA	573	498	650	723	724	HSA/kex2
89	2802	pSAC35:GLP-1(7-36(A8G)).IP2.HSA	GLP-1(7-36(A8G)) (SEQ ID NO:698) is fused downstream from the HSA/kex2 leader sequence and upstream from the intervening peptide-2 of proglucagon peptide and upstream from mature HSA.	pScNHSA	574	499	651			HSA/kex2
90	2803	pSAC35:GLP-1(7-36(A8G))x2.HSA	GLP-1(7-36(A8G)) (SEQ ID NO:698) is tandemly repeated and fused downstream of the HSA/kex2 signal sequence, and upstream of mature HSA.	pScCHSA	419	412	426	433	434	HSA/kex2
91	2804	pSAC35:coGLP-1(7-36(A8G))x2.HSA	GLP-1(7-36(A8G)) (SEQ ID NO:698) is tandemly repeated and fused downstream of the HSA/kex2 signal sequence, and upstream of mature HSA.	pScCHSA	420	413	427	435	436	HSA/kex2
92	2821	pSac35.delKex2.Insulin(GYG).HSA	Synthetic gene coding for a single-chain insulin with HSA at C-terminus. The kex2 site has been deleted from the HSA/KEX2 signal peptide.	pScCHSA	575	500	652			Modified HSA/kex2, lacking the Kex2 site.
93	2822	pSac35.alphaMF.Insulin(GYG).HSA	Synthetic gene coding for a single-chain insulin with HSA at C-terminus. The signal peptide of alpha mating factor (MFα-1) is used for this construct.	pSAC35	576	501	653	725	726	MFα-1
94	2825	pSAC35:HSA.Somatostatin(S14)	14 amino acid peptide of Somatostatin was fused downstream of HSA/kex2	pScNHSA	577	502	654	727	728	HSA/kex2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			leader and mature HSA.							
95	2830	pSAC35:S28.HSA	28 amino acids of somatostatin fused downstream of HSA/kex2 leader and upstream of mature HSA.	pScCHSA	578	503	655	729	730	HSA/kex2
96	2831	pSAC35:HSA.S28	28 amino acids of somatostatin fused downstream of HSA/kex2 leader and mature HSA.	pScNHSA	579	504	656	731	732	HSA/kex2
97	2832	pSAC35:Insulin.HSA (yeast codon optimized)	Long-acting insulin peptide fused upstream of mature HSA.	pScCHSA	580	505	657	733	734	invertase
98	2872	pSAC35:HSA.IFNaA (C1-Q91)/ D(L93-E166)	This construct contains a hybrid form of IFNaA and IFNaD fused downstream of mature HSA.	pSAC35	455	456	457	458	459	HSA/kex2
99	2873	pSAC35:HSA.IFNaA (C1-Q91)/ B(L93-E166)	This construct contains a hybrid form of IFNaA and IFNaB fused downstream of mature HSA.	pSAC35	460	461	462	463	464	HSA/kex2
100	2874	pSAC35:HSA.IFNaA (C1-Q91)/ F(L93-E166)	This construct contains a hybrid form of IFNaA and IFNaF fused downstream of mature HSA.	pSAC35	465	466	467	468	469	HSA/kex2
101	2875	pSAC35:HSA.IFNaA (C1Q-62)/D(Q64-E166)	This construct contains a hybrid form of IFNaA and IFNaD fused downstream of mature HSA.	pSAC35	470	471	472	473	474	HSA/kex2
102	2876	pSAC35:HSA.IFNaA (C1-Q91)/ D(L93-E166); R23K,A113V	This construct contains a hybrid form of IFNaA and IFNaD fused downstream of mature HSA.	pSAC35	475	476	477	478	479	HSA/kex2
103	2877	pSAC35:KT.Insulin. HSA	Killer toxin signal peptide fused to synthetic gene coding for a single-chain insulin with C-terminal HSA	pScCHSA	581	506	658	735	736	Killer toxin
104	2878	pSAC35:AP.Insulin. HSA	Acid phospatase signal peptide fused to synthetic gene coding for a single-chain insulin with C-terminal HSA.	pSAC35	582	507	659			Acid phosphatase

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
105	2882	pSac35.alphaMFprepro.Insulin(GYG).HSA	MFα-1 prepro signal followed by GYG insulin followed by mature HSA.	pSAC35	583	508	660			MFα-1
106	2885	pSac35.alphaMFpreproEEA.Insulin(GYG).HSA	Yeast MFα-1 prepro signal followed by GYG insulin follwed by mature HSA.	pSAC35	584	509	661			Yeast MFα-1
107	2891	pGAP.alphaMF.Insulin(GYG).HSA	Synthetic gene coding for a single-chain insulin with HSA at C-terminus. The signal peptide of HSA/kex2 is used for this construct.	pYPGaf	585	510	662	737	738	HSA/kex2
108	2897	pGAP.Insulin(KR.GGG.KR).HSA	Long-acting insulin analog using a synthetic gene coding for a single-chain insulin with HSA at C-terminus. Contains a modified loop for processing resulting in correctly disulfide bonded insulin coupled to HSA	pYPGaf	586	511	663	739	740	HSA/kex2
109	2900	pSAC:GLP-1(7-36)x2.HSA	GLP-1(7-36) is tandemly repeated and then fused downstream of the HSA/kex2 signal sequence and upstream of mature HSA.	pScCHSA	421	414	428	437	438	HSA/kex2
110	2901	pSAC35:IL22.A18-P202.HSA	Amino acids A18-P202 of IL22 fused downstream of HSA/kex2 leader and upstream of mature HSA.	pSAC35	587	512	664	741	742	HSA/kex2
111	2902	pSAC35: Somatostatin(S14(A-G)).HSA	A 14 amino acid peptide of Somatostatin, an inhibitor of growth hormone, synthesized as a C-terminal HSA fusion. Somatostatin has an alanine to glycine change at amino acid 1 of SEQ ID NO:665.	pScCHSA	588	513	665	743	744	HSA/kex2
112	2903	pSAC35:HSA.A18-	Amino acids A18-P202 of IL22	pSAC35	589	514	666	745	746	HSA

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
		P202.IL22	fused downstream of full length HSA.							
113	2904	pSAC35:GLP-1(9-36).GLP-1(7-36).HSA	Amino acids E100 to R127 of preproglucagon (SEQ ID NO:429) (hereinafter, this particular mutant is referred to as GLP-1(9-36)) is fused downstream from the HSA/kex2 signal sequence and upstream from GLP-1(7-36), and mature HSA.	pScCHSA	422	415	429	439	440	HSA/kex2
114	2908	pSAC35:HSA.HCE1P80	Mature HSA fused downstream of the HSA/kex2 leader and upstream of HCE1P80.	pSAC35	590	515	667	747	748	HSA/kex2
115	2909	pSAC35:HSA.HDRMI82	Mature HSA fused downstream of the HSA/kex2 leader sequence and upstream of HDRMI82.	pSAC35	591	516	668	749	750	HSA/kex2
116	2910	pSAC35:HSA.RegIV	Mature HSA fused downstream of the HSA/kex2 leader sequence and upstream of RegIV.	pSAC35	592	517	669	751	752	HSA/kex2
117	2930	pC4.MPIF.Insulin(GYG).HSA	Insulin is downstream of an MPIF signal peptide and upstream of mature HSA.	pC4	593	518	670	753	754	MPIF
118	2931	pC4.HSA.Insulin(GYG)	Synthetic gene coding for a mature single-chain insulin fused downstream of the modified HSA A14 leader and mature HSA.	pC4	594	519	671	755	756	Modified HSA (A14) leader
119	2942	pSac35.TA57.Insulin (GYG).HSA	The TA57 Propeptide fused to a single chain insulin (GYG), and then mature HSA.	pScNHSA	595	520	672	757	758	TA57 propeptide
120	2945	pSAC35:GLP-1(7-36(A8S)).GLP-1(7-36).HSA	Amino acids H98 to R127 of preproglucagon (SEQ ID NO:430) is mutated at position 99 from alanine to serine (hereinafter, this particular	pScCHSA	423	416	430	441	442	HSA/kex2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			mutant is referred to as GLP-1(7-36(A8S)), which is fused downstream from the HSA/kex2 signal sequence and upstream from GLP-1(7-36), and mature HSA.							
121	2964	pSAC35:GLP-1(7-36)x2.HSA	GLP-1(7-36) is tandemly repeated as a dimer and fused downstream from the HSA/kex2 leader sequence and upstream from mature HSA.	pSAC35	424	417	431	443	444	HSA/kex2
122	2982	pSAC35:GLP-1(7-36(A8G).GLP-1(7-36).HSA	GLP-1(7-36(A8G)) (SEQ ID NO:698) is fused downstream from the HSA/kex2 signal sequence and upstream from GLP-1(7-36) and mature HSA.	pScCHSA	425	418	432	445	446	HSA/kex2
123	2986	pSac35.y3SP.TA57PP.Insulin(GYG).HSA	The TA57 Propeptide fused to a single chain insulin (GYG), and then mature HSA.	pScCHSA	596	521	673	759	760	TA57 propeptide
124	3025	pSAC35:INU.Insulin.HSA	Inulinase signal peptide is fused upstream of single chain insulin (GYG) and HSA.	pScCHSA	597	522	674	761	762	inulinase
125	3027	pSAC35:INV.GLP-1(7-36A8G)x2.HSA	Invertase signal peptide followed by GLP-1(7-36(A8G)) (SEQ ID NO:698) tandemly repeated as a dimer, followed by mature HSA.	pSAC35	598	523	675	763	764	invertase
126	3028	pSAC35:INV.GLP-1(7-36(A8G)).GLP-1(7-36).HSA	Invertase signal peptide followed by GLP-1(7-36(A8G)) (SEQ ID NO:698), then GLP-1(7-36(A8G)), and then mature HSA.	pSAC35	599	524	676	765	766	invertase
127	3045	pSAC35:DeltaKex.GLP-1(7-36A8G)x2.HSA	HSA/kex2 signal sequence, minus the last six amino acids of the leader, is fused to GLP-1(7-36(A8G)) (SEQ ID	pSAC35	600	524	676	767	768	HSA/kex2 last six amino

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			NO:698) which is tandemly repeated as a dimer, followed by mature HSA.							acids
128	3046	pSAC35:Delta Kex.GLP-1(7-36A8G).GLP-1(7-36).HSA	HSA/kex2 signal sequence, minus the last six amino acids of the leader, is fused to GLP-1(7-36(A8G)) (SEQ ID NO:698), GLP-1(7-36), and mature HSA.	pSAC35	601	524	676	769	770	HSA/kex2 last six amino acids
129	3049	pC4.HSA.HCE1P80.D92-L229	Amino acids D92 to L229 of HCE1P80 are fused downstream of the full length HSA.	pC4	602	525	677	771	772	HSA
130	3050	pC4.HSA.HCE1P80.A20-L229	Amino acids A20-L229 of HCE1P80 are fused downstream of the full length human HSA	pC4	603	526	678	773	774	HSA
131	3051	pSAC35.HSA.HCE1P80.D92-L229	Amino acids D92 to L229 of HCE1P80, a member of the C1q family of proteins, are fused downstream of the full length human HSA	pSAC35	604	527	679	775	776	HSA
132	3052	pSAC35.HSA.HCE1P80.A20-L229	Amino acids A20-L229 of HCE1P80 are fused downstream of the full length human HSA	pSAC35	605	528	680	777	778	HSA
133	3053	pC4.HSA.HDALV07.K101-N244	The globular domain of adiponectin (amino acids K101-N244) has been inserted downstream of full length human HSA	pC4	606	529	681	779	780	HSA
134	3055	pSAC35.HSA.HDALV07(GD)	Full length HSA followed by amino acids K101-N244 of HDALV07(GD)/ Adiponectin.	pSAC35	607	530	682	781	782	HSA
135	3056	pSAC35.HSA.HDALV07.MP	Full length HSA followed by amino acids Q18 to N244 of HDALV07.	pSAC35	608	531	683	783	784	HSA
136	3069	pSAC35:INU.GLP-	The inulinase signal sequence is fused	pSAC35	609	532	684	785	786	inulinase

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
		1(7-36(A8G))x2.HSA	to GLP-1(7-36(A8G)) (SEQ ID NO:698), which is tandemly repeated as a dimer and fused to mature HSA.							
137	3070	pSAC35:KT.GLP-1(7-36(A8G))x2.HSA	GLP-1(7-36(A8G)) (SEQ ID NO:698) is tandemly repeated as a dimer and fused upstream from mature HSA and downstream from the killer toxin signal sequence.	pSAC35	447	448	449	450	451	Killer toxin
138	3071	pSAC35:MAF.GLP-1(7-36(A8G))x2.HSA	The yeast mating factor α-1 (hereinafter MFα-1) signal sequence is fused to tandemly repeated copies of GLP-1(7-36(A8G)) (SEQ ID NO:698), which are fused to mature HSA.	pSAC35	610	533	685	787	788	MFα-1
139	3072	pSAC35:AP.GLP-1(7-36(A8G))x2.HSA	The acid phosphatase signal sequence is fused to tandemly repeated copies of GLP-1(7-36(A8G)) (SEQ ID NO:698), which are fused to mature HSA.	pSAC35	611	534	686	789	790	Acid phosphatase
140	3085	pSAC35:MAF.GLP-1(7-36(A8G)).GLP-1(7-36).HSA	The yeast mating factor α-1 (hereinafter MFα-1) signal sequence is fused to GLP-1(7-36(A8G)) (SEQ ID NO:698), GLP-1(7-36), and mature HSA.	pSAC35	612	535	687	791	792	MFα-1
141	3086	pSAC35:INU.GLP-1(7-36(A8G)).GLP-1(7-36).HSA	The inulinase signal sequence is fused to GLP-1(7-36(A8G)) (SEQ ID NO:698), GLP-1(7-36), and mature HSA.	pSAC35	613	536	688	793	794	inulinase
142	3087	pSAC35:AP.GLP-1(7-36(A8G)).GLP-1(7-36).HSA	The acid phosphatase signal sequence is fused to GLP-1(7-36(A8G)) (SEQ ID NO:698), GLP-1(7-36), and	pSAC35	614	537	689	795	796	Acid phosphatase

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			mature HSA.							
143	3088	pSAC35.HSA.C-Peptide	HSA/kex2 signal peptide, followed by HSA, followed by the C-Peptide sequence.	pSAC35	615	538	690	797	798	HSA/kex2
144	3106	pSACHSA.HCBOG68	mature HCBOG68 fused downstream of mature HSA and the HSA/kex2 leader sequence.	pSAC35	616	539	691			HSA/kex2
145	3108	pSAC35HSA.PYY	Mature PYY fused downstream of mature HSA and the HSA/kex2 leader.	pSAC35	617	540	692			HSA/kex2
146	3109	pSAC35HSA.PYY3-36	HSA/kex2 leader followed by mature HSA and then PYY3-36 (SEQ ID NO:693).	pSAC35	618	541	693			HSA/kex2
147	3117	pC4:PYY3-36/HSA	HSA leader followed by PYY3-36 (SEQ ID NO:694) and mature HSA.	pC4	619	542	694	799	800	HSA
148	3118	pSAC35:PYY3-36/HSA	HSA/kex2 leader followed by PYY3-36 (SEQ ID NO:695) and mature HSA.	pSAC35	620	543	695	801	802	HSA/kex2
149	3133	pSac35.ySP.TA57PP.Insulin(GYG).HSA	Variant TA57 propeptide leader followed by single chain insulin, followed by mature HSA.	pSAC35	621	544	696	803	804	TA57 variant 1
150	3134	pSac35.ySP.TA57PP+S.Insulin(GYG).HSA	Variant TA57 propeptide leader followed by single chain insulin, followed by mature HSA.	pSAC35	622	545	697	805	806	TA57 variant 2
151	3140	pSAC35:GLP1(mut)DAHK.HSA	GLP-1(7-36(A8G)) (SEQ ID NO:698) is linked to mature HSA by a 16 amino acid linker derived from the N-terminus of HSA. The HSA/kex2 signal sequence is used.	pSAC35	623	546	698	807	808	HSA/kex2
152	3141	pSAC35:Wnt10b/HSA	HSA/kex2 leader followed by amino acids N29 to K389 of Wnt10b	pSAC35	624	547	699	809	810	HSA/kex2

Fusion No.	Construct ID	Construct Name	Description	Expression Vector	SEQ ID NO:Y	SEQ ID NO:X	SEQ ID NO:Z	SEQ ID NO:A	SEQ ID NO:B	Leader Sequence
			followed by mature HSA.							
153	3149	pSAC35.HSA.C-peptide tandem	Full length HSA fused to amino acids E7 to Q37 of SEQ ID NO:700, tandemly repeated.	pSAC35	625	548	700	811	812	HSA
154	3165	pSAC35:HSA.IFNa also named CID 3165, pSAC35:HSA.INFα	HSA fused upstream of IFNα and downstream of the HSA/kex2 leader.	pSAC35	452	453	454			HSA/kex2
155	3197	pC4.MPIF.Insulin(EAE).HSA	A single-chain insulin is downstream of the MPIF signal peptide and upstream of mature human HSA.	pC4	626	549	701			MPIF
156	3198	pSac35.INV.insulin(EAE).HSA	Single-chain insulin is downstream of the invertase signal peptide and upstream of mature human HSA	pSAC35	627	550	702			invertase
157	3232	pSAC35:CART/HSA	HSA/kex2 leader followed by processed active cocaine-amphetamine regulated transcript (CART) (amino acids V69 through L116) followed by mature HSA.	pSAC35	628	551	703	813	814	HSA/kex2
158	3270	pSAC35:adipokine/HSA	HSA/kex2 leader followed by adipokine followed by mature HSA.	pSAC35	629	552	704	815	816	HSA/kex2
159	3281	pSAC35.PY3-36(x2)/HSA	PYY3-36 tandem repeat (x2) fused upstream of HSA and downstream of the HSA/kex2 signal peptide.	pSAC35	630	553	705	817	818	HSA/kex2
160	3282	pSAC35:HSA/PYY3-36(x2)	PYY3-36 tandem repeat (x2) fused downstream of mature HSA and HSA/kex2 leader.	pSAC35	631	554	706	819	820	HSA/kex2
161	3309	pSAC:KT.GLP-1(7-36(A8G))x2.MSA.E25-A608	Killer toxin leader sequence followed by GLP-1(7-36(A8G) followed by mature mouse serum albumin.	pSAC35	834	833	835	836	837	Killer toxin

[0070] Table 2 provides a non-exhaustive list of polynucleotides which encode an albumin fusion protein of the invention. The first column, "Fusion No." assigns a fusion number to each polynucleotide. Column 2, "Construct ID" provides a unique numerical identifier for the corresponding polynucleotide of the invention. The Construct Ids (or CIDs) may be used to refer to polynucleotides which encode albumin fusion proteins comprising a Therapeutic protein portion corresponding to Therapeutic Protein:X identified in the corresponding row of Table 1. The "Construct Name" column (column 3) provides the name of a given albumin fusion construct.

[0071] The fourth column in Table 2, "Description" provides a general description of a given albumin fusion construct, and the fifth column, "Expression Vector" lists the vector into which the polynucleotide corresponding to a nucleic acid molecule encoding a given albumin fusion protein was cloned. Vectors are known in the art, and are available commercially or described elsewhere. For example, as described in the Examples, an "expression cassette" comprising, or alternatively consisting of, one or more of (1) a polynucleotide encoding a given albumin fusion protein, (2) a leader sequence, (3) a promoter region, and (4) a transcriptional terminator, may be assembled in a convenient cloning vector and subsequently be moved into an alternative vector, such as, for example, an expression vector including, for example, a yeast expression vector or a mammalian expression vector. In one embodiment, for expression in *S. cervisiae*, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pSAC35. In another embodiment, for expression in CHO cells, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pC4. In a further embodiment, a polynucleotide comprising or alternatively consisting of a nucleic acid molecule encoding the Therapeutic protein portion of an albumin fusion protein is cloned into pC4:HSA. In a still further embodiment, for expression in NS0 cells, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pEE12. Other useful cloning and/or expression vectors will be known to the skilled artisan and are within the scope of the invention.

[0072] Column 6, "SEQ ID NO:Y," provides the full length amino acid sequence of representative albumin fusion proteins of the invention. In most instances, SEQ ID NO: Y

shows the unprocessed form of the albumin fusion protein encoded – in otherwords, SEQ ID NO: Y shows the signal sequence, a HSA portion, and a therapeutic portion all encoded by a particular construct. Specifically contemplated by the present invention are all polynucleotides that encode SEQ ID NO: Y. When these polynucleotides are used to express the encoded protein from a cell, the cell's natural secretion and processing steps produces a protein that lacks the signal sequence listed in column 4 and/or 11 of Table 2. The specific amino acid sequence of the listed signal sequence is shown later in the specification or is well known in the art. Thus, most preferred embodiments of the present invention include the albumin fusion protein produced by a cell (which would lack the leader sequence shown in column 4 and/or 11 Table 2). Also most preferred are polypeptides comprising SEQ ID NO:Y without the specific leader sequence listed in column 4 and/or 11 of Table 2. Compositions comprising these two preferred embodiments, including pharmaceutical compositions, are also preferred. Moreover, it is well within the ability of the skilled artisan to replace the signal sequence listed in column 4 and/or 11 of Table 2 with a different signal sequence, such as those described later in the specification to facilitate secretion of the processed albumin fusion protein.

[0073] The seventh column, "SEQ ID NO:X," provides the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of a given albumin fusion protein may be derived. In one embodiment, the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of an albumin fusion protein may be derived comprises the wild type gene sequence encoding a Therapeutic protein shown in Table 1. In an alternative embodiment, the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of an albumin fusion protein may be derived comprises a variant or derivative of a wild type gene sequence encoding a Therapeutic protein shown in Table 1, such as, for example, a synthetic codon optimized variant of a wild type gene sequence encoding a Therapeutic protein.

[0074] The eighth column, "SEQ ID NO:Z," provides a predicted translation of the parent nucleic acid sequence (SEQ ID NO:X). This parent sequence can be a full length parent protein used to derive the particular construct, the mature portion of a parent protein, a variant or fragment of a wild type protein, or an artificial sequence that can be

used to create the described construct. One of skill in the art can use this amino acid sequence shown in SEQ ID NO:Z to determine which amino acid residues of an albumin fusion protein encoded by a given construct are provided by the therapeutic protein. Moreover, it is well within the ability of the skilled artisan to use the sequence shown as SEQ ID NO:Z to derive the construct described in the same row. For example, if SEQ ID NO:Z corresponds to a full length protein, but only a portion of that protein is used to generate the specific CID, it is within the skill of the art to rely on molecular biology techniques, such as PCR, to amplify the specific fragment and clone it into the appropriate vector.

[0075] Amplification primers provided in columns 9 and 10, "SEQ ID NO:A" and "SEQ ID NO:B" respectively, are exemplary primers used to generate a polynucleotide comprising or alternatively consisting of a nucleic acid molecule encoding the Therapeutic protein portion of a given albumin fusion protein. In one embodiment of the invention, oligonucleotide primers having the sequences shown in columns 9 and/or 10 (SEQ ID NOS:A and/or B) are used to PCR amplify a polynucleotide encoding the Therapeutic protein portion of an albumin fusion protein using a nucleic acid molecule comprising or alternatively consisting of the nucleotide sequence provided in column 7 (SEQ ID NO:X) of the corresponding row as the template DNA. PCR methods are well-established in the art. Additional useful primer sequences could readily be envisioned and utilized by those of ordinary skill in the art.

[0076] As shown in Table 3, certain albumin fusion constructs disclosed in this application have been deposited with the ATCC®. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

Table 3

Construct ID	Construct Name	ATCC Deposit No./ Date
2053	pEE12:IFNb-HSA also named pEE12.1:IFNβ-HSA	PTA-3764 Oct. 4, 2001
2054	pEE12:HSA-IFNb	PTA-3941

Construct ID	Construct Name	ATCC Deposit No./ Date
		Dec. 19, 2001
2249	pSAC35:IFNa2-HSA also named pSAC23:IFNα2-HSA	PTA-3763 Oct. 4, 2001
2250	pSAC35:HSA.INSULIN(GYG) also named pSAC35.HSA.INSULING(GYG).F1-N62	PTA-3916 Dec. 07, 2001
2255	pSAC35:INSULIN(GYG).HSA also named pSAC35.INSULING(GYG).F1-N62.HSA	PTA-3917 Dec. 07, 2001
2276	pSAC35:HSA.INSULIN(GGG) also named pSAC35.HSA.INSULING(GGG).F1-N58	PTA-3918 Dec. 07, 2001
2343	pSAC35.INV-IFNA2.HSA	PTA-3940 Dec. 19, 2001
2381	pC4:HSA-IFNa2(C17-E181)	PTA-3942 Dec. 19, 2001
2382	pC4:IFNa2-HSA	PTA-3939 Dec. 19, 2001
2492	pC4.IFNb(deltaM22).HSA	PTA-3943 Dec. 19, 2001
3070	pSAC35:KT.GLP-1(7-36(A8G))x2.HSA	PTA-4671 Sept. 16, 2002
3165	pSAC35:HSA.IFNa also named CID 3165, pSAC35:HSA.INFα	PTA-4670 Sept. 16, 2002

[0077] Albumin fusion constructs may routinely be isolated from the deposit by techniques known in the art and described elsewhere herein.

[0078] "Expression cassettes" containing one or more of (1) a polynucleotide encoding a given albumin fusion protein, (2) a leader sequence, (3) a promoter region, and (4) a transcriptional terminator can routinely be moved or "subcloned" from one vector into another. Fragments to be subcloned may be generated by methods known in the art, such as, for example, pcr amplification (e.g., using oligonucleotide primers having the sequence shown in SEQ ID NO:A or B), and/or restriction enzyme digestion.

[0079] In preferred embodiments, the albumin fusion proteins of the invention are

capable of a therapeutic activity and/or biological activity corresponding to the therapeutic activity and/or biological activity of the therapeutic protein corresponding to the therapeutic protein portion of the albumin fusion protein listed in the corresponding row of Table 1. In further preferred embodiments, the therapeutically active protein portions of the albumin fusion proteins of the invention are fragments or variants of the protein encoded by the sequence shown in SEQ ID NO:X column of Table 2, and are capable of the therapeutic activity and/or biologic activity of the corresponding therapeutic protein.

Polypeptide And Polynucleotide Fragments And Variants

Fragments

[0080] The present invention is further directed to fragments of the therapeutic proteins described in Table 1, albumin proteins, and/or albumin fusion proteins of the invention.

[0081] The present invention is also directed to polynucleotides encoding fragments of the Therapeutic proteins described in Table 1, albumin proteins, and/or albumin fusion proteins of the invention.

[0082] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the Therapeutic protein, albumin protein, and/or albumin fusion protein of the invention, other Therapeutic activities and/or functional activities (e.g., a biological activity (e.g., as provided in Table 1, column 2, for the corresponding therapeutic protein), ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of polypeptides with N-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0083] Accordingly, fragments of a Therapeutic protein corresponding to a Therapeutic

protein portion of an albumin fusion protein of the invention, include the full length protein as well as polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the reference polypeptide (i.e., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0084] In addition, fragments of serum albumin polypeptides corresponding to an albumin protein portion of an albumin fusion protein of the invention, include the full length protein as well as polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the reference polypeptide (i.e., serum albumin, or a serum albumin portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, N-terminal deletions may be described by the general formula m-585, where 585 is a whole integer representing the total number of amino acid residues in serum albumin (SEQ ID NO:327), and m is defined as any integer ranging from 2 to 579. Polynucleotides encoding these polypeptides are also encompassed by the invention. In additional embodiments, N-terminal deletions may be described by the general formula m to 609, where 609 is a whole integer representing the total number of amino acid residues in full length human serum albumin (SEQ ID NO:379), and m is defined as any integer ranging from 2 to 603. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0085] Moreover, fragments of albumin fusion proteins of the invention, include the full length albumin fusion protein as well as polypeptides having one or more residues deleted from the amino terminus of the albumin fusion protein (e.g., an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2; or an albumin fusion protein having the amino acid sequence disclosed in column 6 of Table

2). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in the albumin fusion protein, and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0086] Also as mentioned above, even if deletion of one or more amino acids from the N-terminus or C-terminus of a reference polypeptide (e.g., a Therapeutic protein; serum albumin protein; or albumin fusion protein of the invention) results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., a biological activity (e.g., as provided in Table 1, column 2, for the corresponding therapeutic protein), ability to multimerize, ability to bind a ligand) and/or Therapeutic activities may still be retained. For example the ability of polypeptides with C-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking the N-terminal and/or C-terminal residues of a reference polypeptide retains Therapeutic activity can readily be determined by routine methods described herein and/or otherwise known in the art.

[0087] The present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where q is a whole integer representing the total number of amino acid residues in a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0088] In addition, the present invention provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of an albumin

protein corresponding to an albumin protein portion of an albumin fusion protein of the invention (e.g., serum albumin or an albumin protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to 584, where 584 is the whole integer representing the total number of amino acid residues in serum albumin (SEQ ID NO:327) minus 1. Polynucleotides encoding these polypeptides are also encompassed by the invention. In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to 608, where 608 is the whole integer representing the total number of amino acid residues in serum albumin (SEQ ID NO:379) minus 1. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0089] Moreover, the present invention provides polypeptides having one or more residues deleted from the carboxy terminus of an albumin fusion protein of the invention. In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where q is a whole integer representing the total number of amino acid residues in an albumin fusion protein of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0090] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted reference polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or serum albumin (e.g., SEQ ID NO:327), or an albumin protein portion of an albumin fusion protein of the invention, or an albumin protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or an albumin fusion protein, or an albumin fusion protein encoded by a polynucleotide or albumin fusion construct of the invention) where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0091] The present application is also directed to proteins containing polypeptides at

least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a reference polypeptide sequence (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or serum albumin (e.g., SEQ ID NO:327), or an albumin protein portion of an albumin fusion protein of the invention, or an albumin protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or an albumin fusion protein, or an albumin fusion protein encoded by a polynucleotide or albumin fusion construct of the invention) set forth herein, or fragments thereof. In preferred embodiments, the application is directed to proteins comprising polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to reference polypeptides having the amino acid sequence of N- and C-terminal deletions as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0092] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a Therapeutic activity and/or functional activity (e.g. a biological activity such as that provided in Table 1, column 2, for the corresponding therapeutic protein) of the polypeptide sequence of the Therapeutic protein or serum albumin protein of which the amino acid sequence is a fragment.

[0093] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Variants

[0094] "Variant" refers to a polynucleotide or nucleic acid differing from a reference nucleic acid or polypeptide, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the reference nucleic acid or polypeptide.

[0095] As used herein, "variant", refers to a Therapeutic protein portion of an albumin

fusion protein of the invention, albumin portion of an albumin fusion protein of the invention, or albumin fusion protein of the invention differing in sequence from a Therapeutic protein (e.g. see "therapeutic" column of Table 1), albumin protein, and/or albumin fusion protein, respectively, but retaining at least one functional and/or therapeutic property thereof as described elsewhere herein or otherwise known in the art. Generally, variants are overall very similar, and, in many regions, identical to the amino acid sequence of the Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein, albumin protein corresponding to an albumin protein portion of an albumin fusion protein, and/or albumin fusion protein. Nucleic acids encoding these variants are also encompassed by the invention.

[0096] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the amino acid sequence of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention (e.g., the amino acid sequence of a Therapeutic protein:X disclosed in Table 1; or the amino acid sequence of a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 and 2, or fragments or variants thereof), albumin proteins corresponding to an albumin protein portion of an albumin fusion protein of the invention (e.g., the amino acid sequence of an albumin protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 and 2; the amino acid sequence shown in SEQ ID NO:327; or fragments or variants thereof), and/or albumin fusion proteins. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further polypeptides encompassed by the invention are polypeptides encoded by polynucleotides which hybridize to the complement of a nucleic acid molecule encoding an albumin fusion protein of the invention under stringent hybridization conditions (e.g., hybridization to filter bound DNA in 6X Sodium chloride/Sodium citrate (SSC) at about 45 degrees Celsius, followed by one or more washes in 0.2X SSC, 0.1% SDS at about 50 - 65 degrees Celsius), under highly stringent conditions (e.g., hybridization to filter bound DNA in 6X sodium chloride/Sodium citrate (SSC) at about 45 degrees Celsius, followed by one or more washes in 0.1X SSC, 0.2% SDS at about 68

degrees Celsius), or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989 *Current protocol in Molecular Biology*, Green publishing associates, Inc., and John Wiley & Sons Inc., New York, at pages 6.3.1 - 6.3.6 and 2.10.3). Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0097] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, or substituted with another amino acid. These alterations of the reference sequence may occur at the amino- or carboxy-terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0098] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of an albumin fusion protein of the invention or a fragment thereof (such as a Therapeutic protein portion of the albumin fusion protein or an albumin portion of the albumin fusion protein), can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence,

whichever is shorter.

[0099] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[0100] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually

corrected for. No other manual corrections are to made for the purposes of the present invention.

[0101] The variant will usually have at least 75 % (preferably at least about 80%, 90%, 95% or 99%) sequence identity with a length of normal HA or Therapeutic protein which is the same length as the variant. Homology or identity at the nucleotide or amino acid sequence level is determined by BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin *et al.*, Proc. Natl. Acad. Sci. USA 87: 2264-2268 (1990) and Altschul, J. Mol. Evol. 36: 290-300 (1993), fully incorporated by reference) which are tailored for sequence similarity searching.

[0102] The approach used by the BLAST program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases, see Altschul *et al.*, (Nature Genetics 6: 119-129 (1994)) which is fully incorporated by reference. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff *et al.*, Proc. Natl. Acad. Sci. USA 89: 10915-10919 (1992), fully incorporated by reference). For blastn, the scoring matrix is set by the ratios of M (i.e., the reward score for a pair of matching residues) to N (i.e., the penalty score for mismatching residues), wherein the default values for M and N are 5 and -4, respectively. Four blastn parameters may be adjusted as follows: Q=10 (gap creation penalty); R=10 (gap extension penalty); wink=1 (generates word hits at every winkth position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent Blastp parameter settings were Q=9; R=2; wink=1; and gapw=32. A Bestfit comparison between sequences, available in the GCG package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty) and the equivalent settings in protein comparisons are GAP=8 and LEN=2.

[0103] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host, such as, yeast or *E. coli*).

Functional activity

[0104] "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with the full-length, pro-protein, and/or mature form of a Therapeutic protein. Such functional activities include, but are not limited to, biological activity (e.g., a biological activity as provided in Table 1, column 2, for the corresponding therapeutic protein), antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[0105] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a Therapeutic protein of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present

invention).

[0106] In preferred embodiments, an albumin fusion protein of the invention has at least one biological and/or therapeutic activity associated with the Therapeutic protein portion (or fragment or variant thereof) when it is not fused to albumin.

[0107] The albumin fusion proteins of the invention can be assayed for functional activity (e.g., biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Additionally, one of skill in the art may routinely assay fragments of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein, for activity using assays referenced in its corresponding row of Table 1. Further, one of skill in the art may routinely assay fragments of an albumin protein corresponding to an albumin protein portion of an albumin fusion protein, for activity using assays known in the art and/or as described in the Examples section below.

[0108] For example, in one embodiment where one is assaying for the ability of an albumin fusion protein to bind or compete with a Therapeutic protein for binding to an anti-Therapeutic polypeptide antibody and/or anti-albumin antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0109] In a preferred embodiment, where a binding partner (e.g., a receptor or a ligand) of a Therapeutic protein is identified, binding to that binding partner by an albumin fusion protein which comprises that Therapeutic protein as the Therapeutic protein portion of the

fusion can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of an albumin fusion protein to bind to a substrate(s) of the Therapeutic polypeptide corresponding to the Therapeutic protein portion of the fusion can be routinely assayed using techniques known in the art.

[0110] In an alternative embodiment, where the ability of an albumin fusion protein to multimerize is being evaluated, association with other components of the multimer can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., *supra.*

[0111] In preferred embodiments, an albumin fusion protein comprising all or a portion of an antibody that binds a Therapeutic protein, has at least one biological and/or therapeutic activity (e.g., to specifically bind a polypeptide or epitope) associated with the antibody that binds a Therapeutic protein (or fragment or variant thereof) when it is not fused to albumin. In other preferred embodiments, the biological activity and/or therapeutic activity of an albumin fusion protein comprising all or a portion of an antibody that binds a Therapeutic protein is the inhibition (i.e., antagonism) or activation (i.e., agonism) of one or more of the biological activities and/or therapeutic activities associated with the polypeptide that is specifically bound by antibody that binds a Therapeutic protein.

[0112] Albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be characterized in a variety of ways. In particular, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for the ability to specifically bind to the same antigens specifically bound by the antibody that binds a Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein using techniques described herein or routinely modifying techniques known in the art.

[0113] Assays for the ability of the albumin fusion proteins (e.g., comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to (specifically) bind a specific protein or epitope may be performed in solution (*e.g.*, Houghten, Bio/Techniques

13:412-421(1992)), on beads (*e.g.*, Lam, Nature 354:82-84 (1991)), on chips (*e.g.*, Fodor, Nature 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Albumin fusion proteins comprising at least a fragment or variant of a Therapeutic antibody may also be assayed for their specificity and affinity for a specific protein or epitope using or routinely modifying techniques described herein or otherwise known in the art.

[0114] The albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for cross-reactivity with other antigens (e.g., molecules that have sequence/structure conservation with the molecule(s) specifically bound by the antibody that binds a Therapeutic protein (or fragment or variant thereof) corresponding to the Therapeutic protein portion of the albumin fusion protein of the invention) by any method known in the art.

[0115] Immunoassays which can be used to analyze (immunospecific) binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0116] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF,

aprotinin, sodium vanadate), adding the albumin fusion protein of the invention (*e.g.*, comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding sepharose beads coupled to an anti-albumin antibody, for example, to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the albumin fusion protein to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the albumin fusion protein to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0117] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), applying the albumin fusion protein of the invention (diluted in blocking buffer) to the membrane, washing the membrane in washing buffer, applying a secondary antibody (which recognizes the albumin fusion protein, *e.g.*, an anti-human serum albumin antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[0118] ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the

albumin fusion protein (*e.g.*, comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) of the invention conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound or non-specifically bound albumin fusion proteins, and detecting the presence of the albumin fusion proteins specifically bound to the antigen coating the well. In ELISAs the albumin fusion protein does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes albumin fusion protein) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the albumin fusion protein may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0119] The binding affinity of an albumin fusion protein to a protein, antigen, or epitope and the off-rate of an albumin fusion protein-protein/antigen/epitope interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, ^{3}H or ^{125}I) with the albumin fusion protein of the invention in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the albumin fusion protein for a specific protein, antigen, or epitope and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second protein that binds the same protein, antigen or epitope as the albumin fusion protein, can also be determined using radioimmunoassays. In this case, the protein, antigen or epitope is incubated with an albumin fusion protein conjugated to a labeled compound (*e.g.*, ^{3}H or ^{125}I) in the presence of increasing amounts of an unlabeled second protein that binds the same protein, antigen, or epitope as the albumin fusion protein of the invention.

[0120] In a preferred embodiment, BIAcore kinetic analysis is used to determine the

binding on and off rates of albumin fusion proteins of the invention to a protein, antigen or epitope. BIAcore kinetic analysis comprises analyzing the binding and dissociation of albumin fusion proteins, or specific polypeptides, antigens or epitopes from chips with immobilized specific polypeptides, antigens or epitopes or albumin fusion proteins, respectively, on their surface.

[0121] Antibodies that bind a Therapeutic protein corresponding to the Therapeutic protein portion of an albumin fusion protein may also be described or specified in terms of their binding affinity for a given protein or antigen, preferably the antigen which they specifically bind. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M. More preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6}M, 5×10^{-7} M, 10^{7} M, 5×10^{-8} M or 10^{-8} M. Even more preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, $^{10-12}$ M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has an affinity for a given protein or epitope similar to that of the corresponding antibody (not fused to albumin) that binds a Therapeutic protein, taking into account the valency of the albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) and the valency of the corresponding antibody. In addition, assays described herein (see Examples and Table 1) and otherwise known in the art may routinely be applied to measure the ability of albumin fusion proteins and fragments, variants and derivatives thereof to elicit biological activity and/or Therapeutic activity (either *in vitro* or *in vivo*) related to either the Therapeutic protein portion and/or albumin portion of the albumin fusion protein. Other methods will be known to the skilled artisan and are within the scope of the invention.

Albumin

[0122] As described above, an albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion

or chemical conjugation.

[0123] The terms, human serum albumin (HSA) and human albumin (HA) are used interchangeably herein. The terms, "albumin and "serum albumin" are broader, and encompass human serum albumin (and fragments and variants thereof) as well as albumin from other species (and fragments and variants thereof).

[0124] As used herein, "albumin" refers collectively to albumin protein or amino acid sequence, or an albumin fragment or variant, having one or more functional activities (e.g., biological activities) of albumin. In particular, "albumin" refers to human albumin or fragments thereof (see EP 201 239, EP 322 094 WO 97/24445, WO95/23857) especially the mature form of human albumin as shown in Figure 5A-D and SEQ ID NO:327, or albumin from other vertebrates or fragments thereof, or analogs or variants of these molecules or fragments thereof.

[0125] In preferred embodiments, the human serum albumin protein used in the albumin fusion proteins of the invention contains one or both of the following sets of point mutations with reference to SEQ ID NO:327: Leu-407 to Ala, Leu-408 to Val, Val-409 to Ala, and Arg-410 to Ala; or Arg-410 to A, Lys-413 to Gln, and Lys-414 to Gln (see, e.g., International Publication No. WO95/23857, hereby incorporated in its entirety by reference herein). In even more preferred embodiments, albumin fusion proteins of the invention that contain one or both of above-described sets of point mutations have improved stability/resistance to yeast Yap3p proteolytic cleavage, allowing increased production of recombinant albumin fusion proteins expressed in yeast host cells.

[0126] As used herein, a portion of albumin sufficient to prolong the therapeutic activity or shelf-life of the Therapeutic protein refers to a portion of albumin sufficient in length or structure to stabilize or prolong the therapeutic activity of the protein so that the shelf life of the Therapeutic protein portion of the albumin fusion protein is prolonged or extended compared to the shelf-life in the non-fusion state. The albumin portion of the albumin fusion proteins may comprise the full length of the HA sequence as described above or as shown in Figure 5A-D, or may include one or more fragments thereof that are capable of stabilizing or prolonging the therapeutic activity. Such fragments may be of 10 or more amino acids in length or may include about 15, 20, 25, 30, 50, or more contiguous amino acids from the HA sequence or may include part or all of specific domains of HA.

For instance, one or more fragments of HA spanning the first two immunoglobulin-like domains may be used.

[0127] The albumin portion of the albumin fusion proteins of the invention may be a variant of normal HA. The Therapeutic protein portion of the albumin fusion proteins of the invention may also be variants of the Therapeutic proteins as described herein. The term "variants" includes insertions, deletions and substitutions, either conservative or non conservative, where such changes do not substantially alter one or more of the oncotic, useful ligand-binding and non-immunogenic properties of albumin, or the active site, or active domain which confers the therapeutic activities of the Therapeutic proteins.

[0128] In particular, the albumin fusion proteins of the invention may include naturally occurring polymorphic variants of human albumin and fragments of human albumin, for example those fragments disclosed in EP 322 094 (namely HA (Pn), where n is 369 to 419). The albumin may be derived from any vertebrate, especially any mammal, for example human, cow, sheep, or pig. Non-mammalian albumins include, but are not limited to, hen and salmon. The albumin portion of the albumin fusion protein may be from a different animal than the Therapeutic protein portion.

[0129] Generally speaking, an HA fragment or variant will be at least 100 amino acids long, preferably at least 150 amino acids long. The HA variant may consist of or alternatively comprise at least one whole domain of HA, for example domains 1 (amino acids 1-194 of SEQ ID NO:327), 2 (amino acids 195-387 of SEQ ID NO:327), 3 (amino acids 388-585 of SEQ ID NO:327), 1 + 2 (1-387 of SEQ ID NO:327), 2 + 3 (195-585 of SEQ ID NO:327) or 1 + 3 (amino acids 1-194 of SEQ ID NO:327 + amino acids 388-585 of SEQ ID NO:327). Each domain is itself made up of two homologous subdomains namely 1-105, 120-194, 195-291, 316-387, 388-491 and 512-585, with flexible inter-subdomain linker regions comprising residues Lys106 to Glu119, Glu292 to Val315 and Glu492 to Ala511.

[0130] Preferably, the albumin portion of an albumin fusion protein of the invention comprises at least one subdomain or domain of HA or conservative modifications thereof. If the fusion is based on subdomains, some or all of the adjacent linker is preferably used to link to the Therapeutic protein moiety.

Antibodies that Specifically bind Therapeutic proteins are also Therapeutic proteins

[0131] The present invention also encompasses albumin fusion proteins that comprise at least a fragment or variant of an antibody that specifically binds a Therapeutic protein disclosed in Table 1. It is specifically contemplated that the term "Therapeutic protein" encompasses antibodies that bind a Therapeutic protein (e.g., as Described in column I of Table 1) and fragments and variants thereof. Thus an albumin fusion protein of the invention may contain at least a fragment or variant of a Therapeutic protein, and/or at least a fragment or variant of an antibody that binds a Therapeutic protein.

Antibody structure and background

[0132] The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, 1gG, IgA, and IgE, respectively. *See generally, Fundamental Immunology* Chapters 3-5 (Paul, W., ed., 4th ed. Raven Press, N.Y. (1998)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site.

[0133] Thus, an intact IgG antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are the same.

[0134] The chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDR regions, in general, are the portions of the antibody which make contact with the antigen and determine its specificity. The CDRs from the heavy and the light chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light

and heavy chains variable regions comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The variable regions are connected to the heavy or light chain constant region. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J *Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

[0135] As used herein, "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds an antigen (e.g., a molecule containing one or more CDR regions of an antibody). Antibodies that may correspond to a Therapeutic protein portion of an albumin fusion protein include, but are not limited to, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies (e.g., single chain Fvs), Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies specific to antibodies of the invention), and epitope-binding fragments of any of the above (e.g., VH domains, VL domains, or one or more CDR regions).

Antibodies that bind Therapeutic Proteins

[0136] The present invention encompasses albumin fusion proteins that comprise at least a fragment or variant of an antibody that binds a Therapeutic Protein (e.g., as disclosed in Table 1) or fragment or variant thereof.

[0137] Antibodies that bind a Therapeutic protein (or fragment or variant thereof) may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken antibodies. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries and xenomice or other organisms that have been genetically engineered to produce human antibodies.

[0138] The antibody molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention

can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the antibody molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG1. In other preferred embodiments, the immunoglobulin molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG2. In other preferred embodiments, the immunoglobulin molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG4.

[0139] Most preferably the antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains.

[0140] The antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a Therapeutic protein or may be specific for both a Therapeutic protein as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[0141] Antibodies that bind a Therapeutic protein (or fragment or variant thereof) may be bispecific or bifunctional which means that the antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. *See, e.g.*, Songsivilai & Lachmann *Clin. Exp. Immunol.* 79:

315-321 (1990), Kostelny et al. J *Immunol.* 148:1547 1553 (1992). In addition, bispecific antibodies may be formed as "diabodies" (Holliger et al. "'Diabodies': small bivalent and bispecific antibody fragments" PNAS USA 90:6444-6448 (1993)) or "Janusins" (Traunecker et al. "Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells" *EMBO J* 10:3655-3659 (1991) and Traunecker et al. "Janusin: new molecular design for bispecific reagents" *Int J Cancer Suppl* 7:51-52 (1992)).

[0142] The present invention also provides albumin fusion proteins that comprise, fragments or variants (including derivatives) of an antibody described herein or known elsewhere in the art. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants encode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues.

[0143] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may be described or specified in terms of the epitope(s) or portion(s) of a Therapeutic protein which they recognize or specifically bind. Antibodies which specifically bind a Therapeutic protein or a specific epitope of a Therapeutic protein may also be excluded. Therefore, the present invention encompasses antibodies that specifically bind Therapeutic proteins, and allows for the exclusion of the same. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, binds the same epitopes as the unfused fragment or variant of that antibody.

[0144] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a Therapeutic protein are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% sequence identity (as calculated using methods known in the art and described herein) to a Therapeutic protein are also included in the present invention. In specific embodiments, antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% sequence identity (as calculated using methods known in the art and described herein) to a Therapeutic protein are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has similar or substantially identical cross reactivity characteristics compared to that particular antibody.

[0145] Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide encoding a Therapeutic protein under stringent hybridization conditions (as described herein). Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M. More preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6}M, 5×10^{-7} M, 10^{7} M, 5×10^{-8} M or 10^{-8} M. Even more preferred binding affinities include those with a dissociation

constant or Kd less than 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, $^{10-12}$ M, 5 X 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has an affinity for a given protein or epitope similar to that of the corresponding antibody (not fused to albumin) that binds a Therapeutic protein, taking into account the valency of the albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) and the valency of the corresponding antibody.

[0146] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of a Therapeutic protein as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, competitively inhibits binding of a second antibody to an epitope of a Therapeutic protein as well as the fragment or variant of the antibody comprised by the fusion protein competitively inhibits binding of said second antibody to an epitope of a Therapeutic protein. In other preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, competitively inhibits binding of a second antibody to an epitope of a Therapeutic protein by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[0147] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may act as agonists or antagonists of the Therapeutic protein. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the

phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has similar or substantially similar characteristics with regard to preventing ligand binding and/or preventing receptor activation compared to an un-fused fragment or variant of the antibody that binds the Therapeutic protein.

[0148] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the Therapeutic proteins (e.g. as disclosed in Table 1). The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference

herein in their entireties). In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, have similar or substantially identical agonist or antagonist properties as an un-fused fragment or variant of the antibody that binds the Therapeutic protein.

[0149] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may be used, for example, to purify, detect, and target Therapeutic proteins, including both in *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the Therapeutic protein in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety. Likewise, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, may be used, for example, to purify, detect, and target Therapeutic proteins, including both in *in vitro* and *in vivo* diagnostic and therapeutic methods.

[0150] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids. Albumin fusion proteins of the invention may also be modified as described above.

Methods of Producing Antibodies that bind Therapeutic Proteins

[0151] The antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-

of-interest can be produced by various procedures well known in the art. For example, a Therapeutic protein may be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to; Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0152] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0153] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. In a non-limiting example, mice can be immunized with a Therapeutic protein or fragment or variant thereof or a cell expressing such a Therapeutic protein or fragment or variant thereof. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which

generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0154] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0155] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[0156] In general, the sample containing human B cells is innoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners

for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g, SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[0157] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

[0158] For example, antibodies that bind to a Therapeutic protein can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make antibodies that bind to a Therapeutic protein include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637;

5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0159] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0160] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and

sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0161] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0162] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be

obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181; and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0163] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Polynucleotides Encoding Antibodies

[0164] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a Therapeutic protein, and more preferably, an antibody that binds to a polypeptide having the amino acid sequence of a "Therapeutic protein:X" as disclosed in the "SEQ ID NO: Z"column of Table 2.

[0165] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the

nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0166] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art (See Example 46).

[0167] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0168] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison

to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0169] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[0170] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Recombinant Expression of Antibodies

[0171] Recombinant expression of an antibody, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody or a single chain antibody), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0172] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0173] A variety of host-expression vector systems may be utilized to express the

antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

[0174] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a

fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0175] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0176] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[0177] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion

desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[0178] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[0179] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which

confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu et al., Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0180] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[0181] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807;

WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

[0182] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0183] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

Modifications of Antibodies

[0184] Antibodies that bind a Therapeutic protein or fragments or variants can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag

provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[0185] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc. Other examples of detectable substances have been described elsewhere herein.

[0186] Further, an antibody of the invention may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or

cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0187] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol.*, *6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0188] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride

or polypropylene.

[0189] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0190] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0191] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Antibody-albumin fusion

[0192] Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention include, but are not limited to, antibodies that bind a Therapeutic protein disclosed in the "Therapeutic Protein X" column of Table 1, or a fragment or variant thereof.

[0193] In specific embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH domain. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one,

two or three VH CDRs. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR1. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR2. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR3.

[0194] In specific embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL domain. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one, two or three VL CDRs. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR1. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR2. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR3.

[0195] In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one, two, three, four, five, or six VH and/or VL CDRs.

[0196] In preferred embodiments, the fragment or variant of an antibody that

immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, an scFv comprising the VH domain of the Therapeutic antibody, linked to the VL domain of the therapeutic antibody by a peptide linker such as $(Gly_4Ser)_3$ (SEQ ID NO:378).

Immunophenotyping

[0197] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may be utilized for immunophenotyping of cell lines and biological samples. Therapeutic proteins of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies (or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies (or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

[0198] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e., minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Characterizing Antibodies that bind a Therapeutic Protein and Albumin Fusion Proteins Comprising a Fragment or Variant of an Antibody that binds a Therapeutic Protein

[0199] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may be characterized in a variety of ways. In particular, Albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for the ability to specifically bind to the same antigens specifically bound by the antibody that binds a Therapeutic protein corresponding to the antibody that binds a Therapeutic protein portion of the albumin fusion protein using techniques described herein or routinely modifying techniques known in the art.

[0200] Assays for the ability of the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) to (specifically) bind a specific protein or epitope may be performed in solution (*e.g.*, Houghten, Bio/Techniques 13:412-421(1992)), on beads (*e.g.*, Lam, Nature 354:82-84 (1991)), on chips (*e.g.*, Fodor, Nature 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may also be assayed for their specificity and affinity for a specific protein or epitope using or routinely modifying techniques described herein or otherwise known in the art.

[0201] The albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for cross-reactivity with other antigens (e.g., molecules that have sequence/structure conservation with the molecule(s) specifically bound by the antibody that binds a Therapeutic protein (or fragment or variant thereof) corresponding to the Therapeutic protein portion of the albumin fusion protein of the invention) by any method known in the art.

[0202] Immunoassays which can be used to analyze (immunospecific) binding and

cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0203] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding an antibody of the invention or albumin fusion protein of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding protein A and/or protein G sepharose beads (or beads coated with an appropriate anti-iditoypic antibody or anti-albumin antibody in the case when an albumin fusion protein comprising at least a fragment or variant of a Therapeutic antibody) to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody or albumin fusion protein of the invention to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody or albumin fusion protein to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0204] Western blot analysis generally comprises preparing protein samples,

electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), applying the antibody or albumin fusion protein of the invention (diluted in blocking buffer) to the membrane, washing the membrane in washing buffer, applying a secondary antibody (which recognizes the albumin fusion protein, *e.g.*, an anti-human serum albumin antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[0205] ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody or albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) of the invention conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound or non-specifically bound albumin fusion proteins, and detecting the presence of the antibody or albumin fusion proteins specifically bound to the antigen coating the well. In ELISAs the antibody or albumin fusion protein does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody or albumin fusion protein, respectively) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, antibody or the albumin fusion protein may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as

well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0206] The binding affinity of an albumin fusion protein to a protein, antigen, or epitope and the off-rate of an antibody- or albumin fusion protein-protein/antigen/epitope interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, ^{3}H or ^{125}I) with the antibody or albumin fusion protein of the invention in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody or albumin fusion protein of the invention for a specific protein, antigen, or epitope and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second protein that binds the same protein, antigen or epitope as the antibody or albumin fusion protein, can also be determined using radioimmunoassays. In this case, the protein, antigen or epitope is incubated with an antibody or albumin fusion protein of the invention conjugated to a labeled compound (*e.g.*, ^{3}H or ^{125}I) in the presence of increasing amounts of an unlabeled second protein that binds the same protein, antigen, or epitope as the albumin fusion protein of the invention.

[0207] In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibody or albumin fusion proteins of the invention to a protein, antigen or epitope. BIAcore kinetic analysis comprises analyzing the binding and dissociation of antibodies, albumin fusion proteins, or specific polypeptides, antigens or epitopes from chips with immobilized specific polypeptides, antigens or epitopes, antibodies or albumin fusion proteins, respectively, on their surface.

Therapeutic Uses

[0208] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic

compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein), nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein), albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, and nucleic acids encoding such albumin fusion proteins. The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a Therapeutic protein, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a Therapeutic protein includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0209] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein to an animal, preferably a mammal, and most preferably a human, patient for treating one or more diseases, disorders, or conditions, including but not limited to: neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions., and/or as described elsewhere herein. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a Therapeutic protein and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to

treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a Therapeutic protein, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a Therapeutic protein includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0210] A summary of the ways in which the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be used therapeutically includes binding Therapeutic proteins locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0211] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0212] The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a

preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0213] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against Therapeutic proteins, fragments or regions thereof, (or the albumin fusion protein correlate of such an antibody) for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include dissociation constants or Kd's less than 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M. More preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-5} M, 10^{-5} M, 5 X 10^{-6} M, 10^{-6}M, 5 X 10^{-7} M, 10^{7} M, 5 X 10^{-8} M or 10^{-8} M. Even more preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, $^{10-12}$ M, 5 X 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M.

Gene Therapy

[0214] In a specific embodiment, nucleic acids comprising sequences encoding antibodies that bind therapeutic proteins or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a Therapeutic protein, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0215] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described in more detail elsewhere in this application.

Demonstration of Therapeutic or Prophylactic Activity

[0216] The compounds or pharmaceutical compositions of the invention are preferably

tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, *in vitro* assays which can be used to determine whether administration of a specific compound is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[0217] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0218] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0219] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu et al., J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be

administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0220] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0221] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[0222] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984);

Ranger et al., J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[0223] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0224] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0225] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical

excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0226] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0227] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric

hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0228] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a Therapeutic protein can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0229] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

Diagnosis and Imaging

[0230] Labeled antibodies and derivatives and analogs thereof that bind a Therapeutic protein (or fragment or variant thereof) (including albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein), can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of the Therapeutic protein or fragments or variants thereof. The invention provides for the detection of aberrant expression of a Therapeutic protein, comprising (a) assaying the expression of the Therapeutic protein in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed

Therapeutic protein expression level compared to the standard expression level is indicative of aberrant expression.

[0231] The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the Therapeutic protein in cells or body fluid of an individual using one or more antibodies specific to the Therapeutic protein or albumin fusion proteins comprising at least a fragment of variant of an antibody specific to a Therapeutic protein, and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed Therapeutic protein gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0232] Antibodies of the invention or albumin fusion proteins comprising at least a fragment of variant of an antibody specific to a Therapeutic protein can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0233] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a Therapeutic protein or fragment or variant thereof in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: (a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically

binds to the polypeptide of interest; (b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the Therapeutic protein is expressed (and for unbound labeled molecule, to be cleared to background level); (c) determining background level; and (d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the therapeutic protein. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0234] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment, or albumin fusion protein comprising at least a fragment or variant of an antibody that binds a Therapeutic protein will then preferentially accumulate at the location of cells which contain the specific Therapeutic protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0235] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0236] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0237] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used.

Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0238] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI). Antibodies that specifically detect the albumin fusion protein but not albumin or the therapeutic protein alone are a preferred embodiment. These can be used to detect the albumin fusion protein as described throughout the specification.

Kits

[0239] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0240] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or

cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0241] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0242] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0243] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a

suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0244] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0245] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Albumin Fusion Proteins

[0246] The present invention relates generally to albumin fusion proteins and methods of treating (e.g., ameliorating) or preventing a metabolic/endocrine disease or disorder. In other embodiments, the present invention relates to albumin fusion proteins and methods of treating (e.g., ameliorating) or preventing a disease, disorder, and/or condition associated with aberrant insulin secretion and/or action. In a preferred embodiment, the present invention relates to albumin fusion proteins and methods of treating (e.g., ameliorating) or preventing a disease, disorder, and/or condition associated with diabetes. In a highly preferred embodiment, the present invention relates to albumin fusion proteins and methods of treating (e.g., ameliorating) or preventing Type II Non-Insulin-Dependent Diabetes Mellitus (NIDDM) and/or a condition associated with NIDDM. In another highly preferred embodiment, the present invention relates to albumin fusion proteins and methods of treating (e.g., ameliorating) or preventing Type I Insulin-Dependent Diabetes Mellitus (IDDM) and/or a condition associated with IDDM.

[0247] In further embodiments, the present invention relates to albumin fusion proteins and methods of treating (e.g., ameliorating) or preventing a condition including, but not limited to, insulin resistance, insulin sensitivity, hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, hyperketonuria, retinopathy (e.g., diabetic retinopathy),

mononeuropathy, polyneuropathy, atherosclerosis, ulcers, heart disease, stroke, anemia, gangrene (e.g., of the feet and hands), impotence, infection, cataract, poor kidney function, malfunctioning of the autonomic nervous system, impaired white blood cell function, Carpal tunnel syndrome, Dupuytren's contracture, and diabetic ketoacidosis.

[0248] As used herein, "albumin fusion protein" refers to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a Therapeutic protein (or fragment or variant thereof). An albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion (i.e., the albumin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a Therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of albumin). The Therapeutic protein and albumin protein, once part of the albumin fusion protein, may each be referred to as a "portion", "region" or "moiety" of the albumin fusion protein.

[0249] In a preferred embodiment, the invention provides an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 or Table 2. Polynucleotides encoding these albumin fusion proteins are also encompassed by the invention.

[0250] Preferred albumin fusion proteins of the invention, include, but are not limited to, albumin fusion proteins encoded by a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof); a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof) generated as described in Table 2 or in the Examples; or a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or

variant thereof), further comprising, or alternatively consisting of, for example, one or more of the following elements: (1) a functional self-replicating vector (including but not limited to, a shuttle vector, an expression vector, an integration vector, and/or a replication system), (2) a region for initiation of transcription (e.g., a promoter region, such as for example, a regulatable or inducible promoter, a constitutive promoter), (3) a region for termination of transcription, (4) a leader sequence, and (5) a selectable marker.

[0251] In a preferred embodiment, the invention provides an albumin fusion protein comprising at least one molecule of a Therapeutic protein disclosed in Table 1. In another preferred embodiment, the invention provides an albumin fusion protein comprising at least a fragment or variant of a Therapeutic protein disclosed in Table 1. In a further embodiment, the invention provides an albumin fusion protein comprising a mature polypeptide sequence of a Therapeutic protein disclosed in Table 1. In another preferred embodiment, the invention provides an albumin fusion protein comprising at least one human serum albumin polypeptide sequence. In a further preferred embodiment, the invention provides an albumin fusion protein comprising at least a fragment or variant of human serum albumin. In a still further embodiment, the invention provides an albumin fusion protein comprising a mature human albumin polypeptide sequence. In a preferred embodiment, the invention provides an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2.

[0252] In one embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein (e.g., as described in Table 1) and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a Therapeutic protein and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active variant of a Therapeutic protein and a serum albumin protein. By "biologically active" and/or "therapeutically active" fragment or variant of a Therapeutic protein of the invention is meant a polypeptide that possesses one or more known biological and/or therapeutic activities associated with a therapeutic protein such as one or more of the Therapeutic proteins described herein or otherwise known in the art (e.g., as described in

columns 2 or 4 of Table 1 for a particular reference protein, and/or below under section heading "Biological Activities"). Biological and/or therapeutic activitity of a fusion protein, or a Therapeutic protein, or a fragment or variant thereof, may routinely be determined using assays described herein (e.g., in Table, 1, column 3, and/or the Examples section) and/or by using or routinely modifying assays/methods known in the art. In preferred embodiments, the serum albumin protein component of the albumin fusion protein is the mature portion of serum albumin.

[0253] In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein, and a biologically active and/or therapeutically active fragment of serum albumin. By "biologically active" and/or "therapeutically active" fragment or variant of human serum albumin is meant a polypeptide that possesses one or more known biological and/or therapeutic activities associated with human serum albumin such as maintaining osmolarity (Yeh et al., Proc. Natl. Acad. Sci. USA, 89:1904-1908 (1992)), slow in vivo clearance from the circulation by the liver and, therefore, a long half-life (Yeh et al., Proc. Natl. Acad. Sci. USA, 89:1904-1908 (1992); Waldmann, T.A., Albumin Structure, Function and Uses, pp. 255-273 (1977)), and a carrier. In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a biologically active and/or therapeutically active variant of serum albumin. In a preferred embodiment, the Therapeutic protein portion of the albumin fusion protein is the mature portion of the Therapeutic protein.

[0254] In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment or variant of a Therapeutic protein and a biologically active and/or therapeutically active fragment or variant of serum albumin. In a preferred embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, the mature portion of a Therapeutic protein and the mature portion of serum albumin.

[0255] In a preferred embodiment, the albumin fusion protein comprises HA as the N-terminal portion, and a Therapeutic protein as the C-terminal portion. In alternative preferred embodiments, an albumin fusion protein comprises HA as the C-terminal portion, and a Therapeutic protein as the N-terminal portion may also be used.

[0256] In another embodiment, the albumin fusion protein has a Therapeutic protein fused to both the N-terminus and the C-terminus of albumin. In one embodiment, the Therapeutic proteins fused at the N- and C- termini are the same Therapeutic protein. In another embodiment, the fragments or variants of Therapeutic proteins fused at the N- and C- termini are from the same Therapeutic protein. In an alternative embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins. In a preferred embodiment, where the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins, these Therapeutic proteins are useful in treating or preventing the same or related disease, disorder, or condition (e.g. as listed in the "Preferred Indication Y" column of Table 1). In another preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins which may be used to treat (e.g., ameliorate) or prevent diseases or disorders (e.g. as listed in the "Preferred Indication Y" column of Table 1) which are known in the art to commonly occur in patients simultaneously, concurrently, or consecutively, and/or which commonly occur in patients in association with one another.

[0257] For example, albumin fusion proteins of the invention containing multiple Therapeutic protein portions fused at the N- and C- termini of albumin may include, but are not limited to, GLP1-HSA-GLP-1, GLP1-HSA-Exendin 4, Exendin 4-HSA-Exendin 4, Exendin 4-HSA-GLP1, GLP1-HSA-Insulin, Exendin 4-HSA-Insulin, Insulin-HSA-Insulin, Insulin-HSA-GLP1, Insulin-HSA-Exendin 4, GLP1-HSA-Resistin, Exendin 4-HSA-Resistin, Insulin-HSA-Resistin, Resistin-HSA-Resistin, Resistin-HSA-GLP1, Resistin-HSA-Exendin 4, Resistin-HSA-Insulin, GLP1-HSA-Leptin, Exendin 4-HSA-Leptin, Insulin-HSA-Leptin, Resistin-HSA-Leptin, Leptin-HSA-Leptin, Leptin-HSA-GLP1, Leptin-HSA-Exendin 4, Leptin-HSA-Insulin, Leptin-HSA-Resistin, GLP1-HSA-IGF1, IGF1-HSA-IGF1, Exendin 4-HSA-IGF1, Insulin-HSA-IGF1, Resistin-HSA–IGF1, Leptin-HSA–IGF1, IGF1-HSA-GLP1, IGF1-HSA-Exendin 4, IGF1-HSA-Insulin, IGF1-HSA-Resistin, IGF1-HSA-Leptin, HCEIP80-HSA-HCEIP80, IGF1-HSA-HCEIP80, GLP1-HSA-HCEIP80, Exendin 4-HSA-HCEIP80, Insulin-HSA-HCEIP80, Resistin-HSA-HCEIP80, Leptin-HSA-HCEIP80, HCEIP80-HSA-IGF1, HCEIP80-HSA-GLP1, HCEIP80-HSA-Exendin 4, HCEIP80-HSA-Insulin, HCEIP80-HSA-Resistin, HCEIP80-HSA-Leptin, HCEIP80-HSA-HLDOU18, IGF1-HSA-HLDOU18, GLP1-HSA-

HLDOU18, Exendin 4-HSA-HLDOU18, Insulin-HSA-HLDOU18, Resistin-HSA-HLDOU18, Leptin-HSA-HLDOU18, HLDOU18-HSA-HCEIP80, HLDOU18-HSA-IGF1, HLDOU18-HSA-GLP1, HLDOU18-HSA-Exendin 4, HLDOU18-HSA-Insulin, HLDOU18-HSA-Resistin, HLDOU18-HSA-Leptin, and HLDOU18-HSA-HLDOU18, HCEIP80-HSA-RegIV, IGF1-HSA-RegIV, GLP1-HSA-RegIV, Exendin 4-HSA-RegIV, Insulin-HSA-RegIV, Resistin-HSA-RegIV, Leptin-HSA-RegIV, HLDOU18-HSA-RegIV, RegIV-HSA-HCEIP80, RegIV-HSA-IGF1, RegIV-HSA-GLP1, RegIV-HSA-Exendin 4, RegIV-HSA-Insulin, RegIV-HSA-Resistin, RegIV-HSA-Leptin, RegIV-HSA-HLDOU18, RegIV-HSA-RegIV, HCEIP80-HSA-HDRMI82, IGF1-HSA-HDRMI82, GLP1-HSA-HDRMI82, Exendin 4-HSA-HDRMI82, Insulin-HSA-HDRMI82, Resistin-HSA-HDRMI82, Leptin-HSA-HDRMI82, HLDOU18-HSA-HDRMI82, RegIV-HSA-HDRMI82, HDRMI82-HSA-HCEIP80, HDRMI82-HSA-IGF1, HDRMI82-HSA-GLP1, HDRMI82-HSA-Exendin 4, HDRMI82-HSA-Insulin, HDRMI82-HSA-Resistin, HDRMI82-HSA-Leptin, HDRMI82-HSA-HLDOU18, HDRMI82-HSA-RegIV, HDRMI82-HSA-HDRMI82, HCEIP80-HSA-IFNa, IGF1-HSA-IFNa, GLP1-HSA-IFNa, Exendin 4-HSA-IFNa, Insulin-HSA-IFNa, Resistin-HSA-IFNa, Leptin-HSA-IFNa, HLDOU18-HSA-IFNa, RegIV-HSA-IFNa, HDRMI82-HSA-IFNa, IFNa-HSA-HCEIP80, IFNa-HSA-IGF1, IFNa-HSA-GLP1, IFNa-HSA-Exendin 4, IFNa-HSA-Insulin, IFNa-HSA-Resistin, IFNa-HSA-Leptin, IFNa-HSA-HLDOU18, IFNa-HSA-RegIV, IFNa-HSA-HDRMI82, IFNa-HSA-IFNa, IL22-HSA-IL-22, IL22-HSA-insulin, IL22-HSA-GLP-1, IL22-HSA-Exendin-4, IL22-HSA-HLDOU18, IL22-HSA-Resistin, IL22-HSA-Leptin, IL22-HSA-HCEIP80, IL22-HSA-IGF1, IL22-HSA-IFNa, IL22-HSA-RegIV, IL22-HSA-HDRMI82, insulin-HSA-IL22, GLP1-HSA-IL22, Exendin-4-HSA-IL22, HLDOU18-HSA-IL22, Resistin-HSA-IL22, Leptin-HSA-IL22, HCEIP80-HSA-IL22, IGF1-HSA-IL22, IFNa-HSA-IL22, RegIV-HSA-IL22, and HDRMI82-HSA-IL22.

[0258] Albumin fusion proteins of the invention encompass proteins containing one, two, three, four, or more molecules of a given Therapeutic protein X or variant thereof fused to the N- or C- terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof. Molecules of a given Therapeutic protein X or variants thereof may be in any number of orientations, including, but not limited to, a 'head to head' orientation (e.g., wherein the N-terminus of one molecule of a

Therapeutic protein X is fused to the N-terminus of another molecule of the Therapeutic protein X), or a 'head to tail' orientation (e.g., wherein the C-terminus of one molecule of a Therapeutic protein X is fused to the N-terminus of another molecule of Therapeutic protein X).

[0259] In one embodiment, one, two, three, or more tandemly oriented Therapeutic protein X polypeptides (or fragments or variants thereof) are fused to the N- or C-terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof.

[0260] In a specific embodiment, one, two, three, four, five, or more tandemly oriented molecules of GLP1 are fused to the N- or C-terminus of albumin or variant thereof. For example, one, two, three, four, five, or more tandemly oriented molecules of GLP1 (including, but not limited to, molecules of GLP1 comprising, or alternatively consisting of, amino acids His-98 to Arg-127) are fused to the N- or C-terminus of albumin or variant thereof. Exemplary fusion proteins of the invention containing multiple protein portions of GLP1, include, but are not limited to, GLP1-GLP1-HSA, HSA-GLP1-GLP1, GLP1-GLP1-GLP1-HSA, HSA-GLP1-GLP1-GLP1, GLP1-GLP1-GLP1-GLP1-HSA, HSA-GLP1-GLP1-GLP1-GLP1.

[0261] In another specific embodiment, one, two, three, four, five, or more tandemly oriented molecules of GLP-1 are fused to the N- or C-terminus of albumin or variant thereof. For example, one, two, three, four, five, or more tandemly oriented molecules of GLP-1 (including, but not limited to, molecules of GLP-1 comprising, or alternatively consisting of, amino acids 7 to 36, with residue 8 being mutated from an Alanine to a Glycine) (See for Example, the mutants disclosed in U.S. Patent No. 5,545,618, herein incorporated by reference in its entirety) are fused to the N- or C-terminus of albumin or variant thereof. Exemplary fusion proteins of the invention containing multiple protein portions of GLP-1, include, but are not limited to, GL1-GLP1-HSA, HSA-GLP1-GLP1, GLP1mutant-GLP1mutant-HSA, HSA-GLP1mutant-GLP1mutant, GLP1mutant-GLP1-HSA, HSA-GLP1mutant-GLP1, GLP1-GLP1mutant-HSA, or HSA-GLP1-GLP1mutant. Particularly preferred embodiments are GLP-1 tandem fusions such as construct ID #3070 and the protein encoded by such construct.

[0262] Albumin fusion proteins of the invention further encompass proteins containing

one, two, three, four, or more molecules of a given Therapeutic protein X or variant thereof fused to the N- or C- terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof, wherein the molecules are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Albumin fusion proteins comprising multiple Therapeutic protein X polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology. Linkers are particularly important when fusing a small peptide to the large HSA molecule. The peptide itself can be a linker by fusing tandem copies of the peptide (see for example GLP-1) or other known linkers can be used. Constructs that incorporate linkers are described in Table 2 or are apparent when examining SEQ ID NO:Y.

[0263] Further, albumin fusion proteins of the invention may also be produced by fusing a Therapeutic protein X or variants thereof to the N-terminal and/or C-terminal of albumin or variants thereof in such a way as to allow the formation of intramolecular and/or intermolecular multimeric forms. In one embodiment of the invention, albumin fusion proteins may be in monomeric or multimeric forms (i.e., dimers, trimers, tetramers and higher multimers). In a further embodiment of the invention, the Therapeutic protein portion of an albumin fusion protein may be in monomeric form or multimeric form (i.e., dimers, trimers, tetramers and higher multimers). In a specific embodiment, the Therapeutic protein portion of an albumin fusion protein is in multimeric form (i.e., dimers, trimers, tetramers and higher multimers), and the albumin protein portion is in monomeric form.

[0264] In addition to albumin fusion protein in which the albumin portion is fused N-terminal and/or C-terminal of the Therapeutic protein portion, albumin fusion proteins of the invention may also be produced by inserting the Therapeutic protein or peptide of interest (e.g., a Therapeutic protein X as disclosed in Table 1, or an antibody that binds a Therapeutic protein or a fragment or variant thereof) into an internal region of HA. For instance, within the protein sequence of the HA molecule a number of loops or turns exist between the end and beginning of α-helices, which are stabilized by disulphide bonds. The loops, as determined from the crystal structure of HA (PDB identifiers 1AO6, 1BJ5, 1BKE, 1BM0, 1E7E to 1E7I and 1UOR) for the most part extend away from the body of

the molecule. These loops are useful for the insertion, or internal fusion, of therapeutically active peptides, particularly those requiring a secondary structure to be functional, or Therapeutic proteins, to essentially generate an albumin molecule with specific biological activity.

[0265] Loops in human albumin structure into which peptides or polypeptides may be inserted to generate albumin fusion proteins of the invention include: Val54-Asn61, Thr76-Asp89, Ala92-Glu100, Gln170-Ala176, His 247 - Glu252, Glu 266 - Glu277, Glu 280-His288, Ala362-Glu368, Lys439-Pro447, Val462-Lys475, Thr478-Pro486, and Lys560-Thr566. In more preferred embodiments, peptides or polypeptides are inserted into the Val54-Asn61, Gln170-Ala176, and/or Lys560-Thr566 loops of mature human albumin (SEQ ID NO:327).

[0266] Peptides to be inserted may be derived from either phage display or synthetic peptide libraries screened for specific biological activity or from the active portions of a molecule with the desired function. Additionally, random peptide libraries may be generated within particular loops or by insertions of randomized peptides into particular loops of the HA molecule and in which all possible combinations of amino acids are represented.

[0267] Such library(s) could be generated on HA or domain fragments of HA by one of the following methods:

a. randomized mutation of amino acids within one or more peptide loops of HA or HA domain fragments. Either one, more or all the residues within a loop could be mutated in this manner;

b. replacement of, or insertion into one or more loops of HA or HA domain fragments (*i.e.*, internal fusion) of a randomized peptide(s) of length X_n (where X is an amino acid and n is the number of residues;

c. N-, C- or N- and C- terminal peptide/protein fusions in addition to (a) and/or (b).

[0268] The HA or HA domain fragment may also be made multifunctional by grafting the peptides derived from different screens of different loops against different targets into the same HA or HA domain fragment.

[0269] In preferred embodiments, peptides inserted into a loop of human serum

albumin are peptide fragments or peptide variants of the Therapeutic proteins disclosed in Table 1. More particularly, the invention encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids in length inserted into a loop of human serum albumin. The invention also encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids fused to the N-terminus of human serum albumin. The invention also encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7 at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids fused to the C-terminus of human serum albumin. For example, short peptides described in Table 1 and 2 (e.g., Therapeutic Y) can be inserted into the albumin loops.

[0270] Generally, the albumin fusion proteins of the invention may have one HA-derived region and one Therapeutic protein-derived region. Multiple regions of each protein, however, may be used to make an albumin fusion protein of the invention. Similarly, more than one Therapeutic protein may be used to make an albumin fusion protein of the invention. For instance, a Therapeutic protein may be fused to both the N- and C-terminal ends of the HA. In such a configuration, the Therapeutic protein portions may be the same or different Therapeutic protein molecules. The structure of bifunctional albumin fusion proteins may be represented as: X-HA-Y or Y-HA-X.

[0271] For example, an anti-BLyS™ scFv-HA-IFNα-2b fusion may be prepared to modulate the immune response to IFNα-2b by anti-BLyS™ scFv. An alternative is making a bi (or even multi) functional dose of HA-fusions *e.g.* HA-IFNα-2b fusion mixed with HA-anti-BLyS™ scFv fusion or other HA-fusions in various ratio's depending on function, half-life etc.

[0272] Bi- or multi-functional albumin fusion proteins may also be prepared to target the Therapeutic protein portion of a fusion to a target organ or cell type via protein or peptide at the opposite terminus of HA.

[0273] As an alternative to the fusion of known therapeutic molecules, the peptides

could be obtained by screening libraries constructed as fusions to the N-, C- or N- and C-termini of HA, or domain fragment of HA, of typically 6, 8, 12, 20 or 25 or X_n (where X is an amino acid (aa) and n equals the number of residues) randomized amino acids, and in which all possible combinations of amino acids were represented. A particular advantage of this approach is that the peptides may be selected *in situ* on the HA molecule and the properties of the peptide would therefore be as selected for rather than, potentially, modified as might be the case for a peptide derived by any other method then being attached to HA.

[0274] Additionally, the albumin fusion proteins of the invention may include a linker peptide between the fused portions to provide greater physical separation between the moieties and thus maximize the accessibility of the Therapeutic protein portion, for instance, for binding to its cognate receptor. The linker peptide may consist of amino acids such that it is flexible or more rigid.

[0275] The linker sequence may be cleavable by a protease or chemically to yield the growth hormone related moiety. Preferably, the protease is one which is produced naturally by the host, for example the *S. cerevisiae* protease *kex2* or equivalent proteases.

[0276] Therefore, as described above, the albumin fusion proteins of the invention may have the following formula R1-L-R2; R2-L-R1; or R1-L-R2-L-R1, wherein R1 is at least one Therapeutic protein, peptide or polypeptide sequence, and not necessarily the same Therapeutic protein, L is a linker and R2 is a serum albumin sequence.

[0277] In preferred embodiments, Albumin fusion proteins of the invention comprising a Therapeutic protein have extended shelf life compared to the shelf life the same Therapeutic protein when not fused to albumin. Shelf-life typically refers to the time period over which the therapeutic activity of a Therapeutic protein in solution or in some other storage formulation, is stable without undue loss of therapeutic activity. Many of the Therapeutic proteins are highly labile in their unfused state. As described below, the typical shelf-life of these Therapeutic proteins is markedly prolonged upon incorporation into the albumin fusion protein of the invention.

[0278] Albumin fusion proteins of the invention with "prolonged" or "extended" shelf-life exhibit greater therapeutic activity relative to a standard that has been subjected to the same storage and handling conditions. The standard may be the unfused full-length

Therapeutic protein. When the Therapeutic protein portion of the albumin fusion protein is an analog, a variant, or is otherwise altered or does not include the complete sequence for that protein, the prolongation of therapeutic activity may alternatively be compared to the unfused equivalent of that analog, variant, altered peptide or incomplete sequence. As an example, an albumin fusion protein of the invention may retain greater than about 100% of the therapeutic activity, or greater than about 105%, 110%, 120%, 130%, 150% or 200% of the therapeutic activity of a standard when subjected to the same storage and handling conditions as the standard when compared at a given time point.

[0279] Shelf-life may also be assessed in terms of therapeutic activity remaining after storage, normalized to therapeutic activity when storage began. Albumin fusion proteins of the invention with prolonged or extended shelf-life as exhibited by prolonged or extended therapeutic activity may retain greater than about 50% of the therapeutic activity, about 60%, 70%, 80%, or 90% or more of the therapeutic activity of the equivalent unfused Therapeutic protein when subjected to the same conditions.

Expression of Fusion Proteins

[0280] A particular embodiment of the invention comprises a DNA construct encoding a signal sequence effective for directing secretion in yeast, particularly a yeast-derived signal sequence (especially one which is homologous to the yeast host), and the fused molecule of the first aspect of the invention, there being no yeast-derived pro sequence between the signal and the mature polypeptide.

[0281] As discussed herein, an albumin fusion protein comprising a leader sequence may be secreted from a host cell and may be processed into a mature form by host cell machinery. In one embodiment, prior to protein processing, the albumin fusion protein of the invention may comprise the wild type signal sequence of a given Therapeutic protein portion. In a further embodiment, prior to protein processing, the albumin fusion protein of the invention may comprise the wild type signal sequence of HSA. In another embodiment, prior to protein processing, the albumin fusion protein of the invention may contain a chimeric signal sequence. In a preferred embodiment, the chimeric signal sequence comprises, or alternatively consists of, the full length HSA signal sequence or a portion thereof. In a further embodiment, prior to protein processing, the albumin fusion

protein of the invention may contain the wild type signal sequence of invertase, "INV". In an additional embodiment, prior to protein processing, the albumin fusion protein of the invention may contain the wild type signal sequence of mating factor alpha, "MAF". In a still further embodiment, prior to protein processing, the albumin fusion protein of the invention may contain the wild type signal sequence of Myeloid Progenitor Inhibitory Factor, "MPIF" (see GenBank Accession Number AAB51134).

[0282] The *Saccharomyces cerevisiae* invertase signal is a preferred example of a yeast-derived signal sequence.

[0283] Conjugates of the kind prepared by Poznansky *et al.*, (FEBS Lett. 239:18 (1988)), in which separately-prepared polypeptides are joined by chemical cross-linking, are not contemplated.

[0284] The present invention also includes a cell, preferably a yeast cell transformed to express an albumin fusion protein of the invention. In addition to the transformed host cells themselves, the present invention also contemplates a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a monoclonal culture, in a nutrient medium. If the polypeptide is secreted, the medium will contain the polypeptide, with the cells, or without the cells if they have been filtered or centrifuged away. Many expression systems are known and may be used, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*, *Kluyveromyces lactis* and *Pichia pastoris*, filamentous fungi (for example *Aspergillus*), plant cells, animal cells and insect cells.

[0285] Preferred yeast strains to be used in the production of albumin fusion proteins are D88, DXY1 and BXP10. D88 [*leu2-3*, *leu2-122*, *can1*, *pra1*, *ubc4*] is a derivative of parent strain AH22*his*$^+$ (also known as DB1; see, e.g., Sleep *et al.* Biotechnology 8:42-46 (1990)). The strain contains a *leu2* mutation which allows for auxotrophic selection of 2 micron-based plasmids that contain the LEU2 gene. D88 also exhibits a derepression of PRB1 in glucose excess. The PRB1 promoter is normally controlled by two checkpoints that monitor glucose levels and growth stage. The promoter is activated in wild type yeast upon glucose depletion and entry into stationary phase. Strain D88 exhibits the repression by glucose but maintains the induction upon entry into stationary phase. The PRA1 gene encodes a yeast vacuolar protease, YscA endoprotease A, that is localized in the ER. The

UBC4 gene is in the ubiquitination pathway and is involved in targeting short lived and abnormal proteins for ubiquitin dependant degradation. Isolation of this ubc4 mutation was found to increase the copy number of an expression plasmid in the cell and cause an increased level of expression of a desired protein expressed from the plasmid (see, e.g., International Publication No. WO99/00504, hereby incorporated in its entirety by reference herein).

[0286] DXY1, a derivative of D88, has the following genotype: [*leu2-3, leu2-122, can1, pra1, ubc4, ura3::yap3*]. In addition to the mutations isolated in D88, this strain also has a knockout of the YAP3 protease. This protease causes cleavage of mostly di-basic residues (RR, RK, KR, KK) but can also promote cleavage at single basic residues in proteins. Isolation of this yap3 mutation resulted in higher levels of full length HSA production (see, e.g., U.S. Patent No. 5,965,386 and Kerry-Williams et al., Yeast 14:161-169 (1998), hereby incorporated in their entireties by reference herein).

[0287] BXP10 has the following genotype: *leu2-3, leu2-122, can1, pra1, ubc4, ura3, yap3::URA3, lys2, hsp150::LYS2, pmt1::URA3.* In addition to the mutations isolated in DXY1, this strain also has a knockout of the PMT1 gene and the HSP150 gene. The PMT1 gene is a member of the evolutionarily conserved family of dolichyl-phosphate-D-mannose protein O-mannosyltransferases (Pmts). The transmembrane topology of Pmt1p suggests that it is an integral membrane protein of the endoplasmic reticulum with a role in O-linked glycosylation. This mutation serves to reduce/eliminate O-linked glycosylation of HSA fusions (see, e.g., International Publication No. WO00/44772, hereby incorporated in its entirety by reference herein). Studies revealed that the Hsp150 protein is inefficiently separated from rHA by ion exchange chromatography. The mutation in the HSP150 gene removes a potential contaminant that has proven difficult to remove by standard purification techniques. See, e.g., U.S. Patent No. 5,783,423, hereby incorporated in its entirety by reference herein.

[0288] The desired protein is produced in conventional ways, for example from a coding sequence inserted in the host chromosome or on a free plasmid. The yeasts are transformed with a coding sequence for the desired protein in any of the usual ways, for example electroporation. Methods for transformation of yeast by electroporation are disclosed in Becker & Guarente (1990) *Methods Enzymol.* 194, 182.

[0289] Successfully transformed cells, *i.e.*, cells that contain a DNA construct of the present invention, can be identified by well known techniques. For example, cells resulting from the introduction of an expression construct can be grown to produce the desired polypeptide. Cells can be harvested and lysed and their DNA content examined for the presence of the DNA using a method such as that described by Southern (1975) *J. Mol. Biol.* 98, 503 or Berent *et al.* (1985) *Biotech.* 3, 208. Alternatively, the presence of the protein in the supernatant can be detected using antibodies.

[0290] Fusion of albumin to the Therapeutic protein may be achieved by genetic manipulation, such that the DNA coding for HA, or a fragment thereof, is joined to the DNA coding for the Therapeutic protein. In one embodiment, an exemplary reference nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of the corresponding albumin fusion protein comprises the wild type sequence encoding a Therapeutic protein shown in Table 1. In an alternative embodiment, an exemplary reference nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of the corresponding albumin fusion protein comprises a variant or derivative of a wild type sequence encoding a Therapeutic protein shown in Table 1, such as, for example, a synthetic codon optimized variant of a wild type coding sequence for a Therapeutic protein. In a further embodiment, oligonucleotide primers may be used in overlapping PCR reactions known in the art to generate mutations within a template DNA sequence. A suitable host is then transformed or transfected with the fused nucleotide sequences, so arranged on a suitable plasmid as to express a fusion polypeptide. The expression may be effected in vitro from, for example, prokaryotic or eukaryotic cells, or in vivo e.g, from a transgenic organism.

[0291] Expression vectors are known in the art, and are available commercially or described herein. For example, as described in the Examples, an "expression cassette" containing one or more of: (1) a polynucleotide encoding a given albumin fusion protein, (2) a leader sequence, (3) a promoter region, and (4) a transcriptional terminator, may be assembled in a convenient cloning vector and subsequently be moved into the appropriate vector. In one embodiment, for expression in S. cervisiae, an expression cassette containing a nucleic acid molecule encoding an albumin fusion protein is cloned into pSAC35. In another embodiment, for expression in CHO cells, an expression cassette

comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pC4. In a further embodiment, a polynucleotide containing a nucleic acid molecule encoding the Therapeutic protein portion of an albumin fusion protein is cloned into pC4:HSA. In a still further embodiment, for expression in NS0 cells, an expression cassette containing a nucleic acid molecule encoding an albumin fusion protein is cloned into pEE12. The invention also encompasses embodiments making use of other vectors and/or host systems that are known in the art and that may be routinely applied to express the albumin fusion proteins of the invention.

[0292] Useful yeast plasmid vectors include pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (YIps) and incorporate the yeast selectable markers HIS3, 7RP1, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps).

[0293] Preferred vectors for making albumin fusion proteins for expression in yeast include pPPC0005, pScCHSA, pScNHSA, and pC4:HSA which are described in detail in Example 2. Figure 3 shows a map of the pPPC0005 plasmid that can be used as the base vector into which polynucleotides encoding Therapeutic proteins may be cloned to form HA-fusions. It contains a *PRB1 S. cerevisiae* promoter (PRB1p), a Fusion leader sequence (FL), DNA encoding HA (rHA) and an *ADH1 S. cerevisiae* terminator sequence. The sequence of the fusion leader sequence consists of the first 19 amino acids of the signal peptide of human serum albumin (SEQ ID NO:410) and the last five amino acids of the mating factor alpha 1 promoter (SLDKR, see EP-A-387 319) which is hereby incorporated by reference in its entirety.

[0294] The plasmids, pPPC0005, pScCHSA, pScNHSA, and pC4:HSA were deposited on April 11, 2001 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 and given accession numbers ATCC PTA-3278, PTA-3276, PTA-3279, and PTA-3277, respectively. Another vector useful for expressing an albumin fusion protein in yeast the pSAC35 vector which is described in Sleep *et al.*, BioTechnology 8:42 (1990) which is hereby incorporated by reference in its entirety. Another yeast promoter that can be used to express the albumin fusion protein is the MET25 promoter. See, for example, Dominik Mumburg, Rolf Muller and Martin Funk.

Nucleic Acids Research, 1994, Vol. 22, No. 25, pp. 5767-5768. The Met25 promoter is 383 bases long (bases –382 to –1) and the genes expressed by this promoter are also known as Met15, Met17, and YLR303W. A preferred embodiment uses the sequence below, where, at the 5' end of the sequence below, the Not 1 site used in the cloning is underlined and at the 3' end, the ATG start codon is underlined:

GCGGCCGCCGGATGCAAGGGTTCGAATCCCTTAGCTCTCATTATTTT
TTGCTTTTTCTCTTGAGGTCACATGATCGCAAAATGGCAAATGGCACGTGAAG
CTGTCGATATTGGGGAACTGTGGTGGTTGGCAAATGACTAATTAAGTTAGTCA
AGGCGCCATCCTCATGAAAACTGTGTAACATAATAACCGAAGTGTCGAAAAG
GTGGCACCTTGTCCAATTGAACACGCTCGATGAAAAAAATAAGATATATATAA
GGTTAAGTAAAGCGTCTGTTAGAAAGGAAGTTTTTCCTTTTTCTTGCTCTCTTG
TCTTTTCATCTACTATTTCCTTCGTGTAATACAGGGTCGTCAGATACATAGATA
CAATTCTATTACCCCCATCCATACAATG (SEQ ID NO:831)

[0295] A variety of methods have been developed to operably link DNA to vectors via complementary cohesive termini. For instance, complementary homopolymer tracts can be added to the DNA segment to be inserted to the vector DNA. The vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric tails to form recombinant DNA molecules.

[0296] Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. The DNA segment, generated by endonuclease restriction digestion, is treated with bacteriophage T4 DNA polymerase or E. coli DNA polymerase I, enzymes that remove protruding, gamma-single-stranded termini with their 3' 5'-exonucleolytic activities, and fill in recessed 3'-ends with their polymerizing activities.

[0297] The combination of these activities therefore generates blunt-ended DNA segments. The blunt-ended segments are then incubated with a large molar excess of linker molecules in the presence of an enzyme that is able to catalyze the ligation of blunt-ended DNA molecules, such as bacteriophage T4 DNA ligase. Thus, the products of the reaction are DNA segments carrying polymeric linker sequences at their ends. These DNA segments are then cleaved with the appropriate restriction enzyme and ligated to an

expression vector that has been cleaved with an enzyme that produces termini compatible with those of the DNA segment.

[0298] Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies Inc, New Haven, CT, USA.

[0299] A desirable way to modify the DNA in accordance with the invention, if, for example, HA variants are to be prepared, is to use the polymerase chain reaction as disclosed by Saiki *et al.* (1988) *Science* 239, 487-491. In this method the DNA to be enzymatically amplified is flanked by two specific oligonucleotide primers which themselves become incorporated into the amplified DNA. The specific primers may contain restriction endonuclease recognition sites which can be used for cloning into expression vectors using methods known in the art.

[0300] Exemplary genera of yeast contemplated to be useful in the practice of the present invention as hosts for expressing the albumin fusion proteins are *Pichia* (Hansenula), *Saccharomyces, Kluyveromyces, Candida, Torulopsis, Torulaspora, Schizosaccharomyces, Citeromyces, Pachysolen, Debaromyces, Metschunikowia, Rhodosporidium, Leucosporidium, Botryoascus, Sporidiobolus, Endomycopsis,* and the like. Preferred genera are those selected from the group consisting of *Saccharomyces, Schizosaccharomyces, Kluyveromyces, Pichia* and *Torulaspora.* Examples of *Saccharomyces spp.* are *S. cerevisiae, S. italicus and S. rouxii.*

[0301] Examples of *Kluyveromyces* spp. are *K. fragilis, K. lactis and K. marxianus.* A suitable *Torulaspora* species is *T. delbrueckii.* Examples of *Pichia* (Hansenula) spp. are *P. angusta* (formerly *H. polymorpha*), *P. anomala* (formerly *H. anomala*) and *P. pastoris.* Methods for the transformation of *S. cerevisiae* are taught generally in EP 251 744, EP 258 067 and WO 90/01063, all of which are incorporated herein by reference.

[0302] Preferred exemplary species of *Saccharomyces* include *S. cerevisiae, S. italicus, S. diastaticus,* and *Zygosaccharomyces rouxii.* Preferred exemplary species of *Kluyveromyces* include *K. fragilis* and *K. lactis.* Preferred exemplary species of *Hansenula* include *H. polymorpha* (now *Pichia angusta*), *H. anomala* (now *Pichia anomala*), and *Pichia capsulata.* Additional preferred exemplary species of *Pichia* include *P. pastoris.* Preferred exemplary species of *Aspergillus* include *A. niger* and *A.*

nidulans. Preferred exemplary species of *Yarrowia* include *Y. lipolytica*. Many preferred yeast species are available from the ATCC. For example, the following preferred yeast species are available from the ATCC and are useful in the expression of albumin fusion proteins: *Saccharomyces cerevisiae* Hansen, teleomorph strain BY4743 *yap3* mutant (ATCC Accession No. 4022731); *Saccharomyces cerevisiae* Hansen, teleomorph strain BY4743 *hsp150* mutant (ATCC Accession No. 4021266); *Saccharomyces cerevisiae* Hansen, teleomorph strain BY4743 *pmt1* mutant (ATCC Accession No. 4023792); *Saccharomyces cerevisiae* Hansen, teleomorph (ATCC Accession Nos. 20626; 44773; 44774; and 62995); *Saccharomyces diastaticus* Andrews et Gilliland ex van der Walt, teleomorph (ATCC Accession No. 62987); *Kluyveromyces lactis* (Dombrowski) van der Walt, teleomorph (ATCC Accession No. 76492); *Pichia angusta* (Teunisson et al.) Kurtzman, teleomorph deposited as *Hansenula polymorpha* de Morais et Maia, teleomorph (ATCC Accession No. 26012); *Aspergillus niger* van Tieghem, anamorph (ATCC Accession No. 9029); *Aspergillus niger* van Tieghem, anamorph (ATCC Accession No. 16404); *Aspergillus nidulans* (Eidam) Winter, anamorph (ATCC Accession No. 48756); and *Yarrowia lipolytica* (Wickerham et al.) van der Walt et von Arx, teleomorph (ATCC Accession No. 201847).

[0303] Suitable promoters for S. cerevisiae include those associated with the PGKI gene, GAL1 or GAL10 genes, CYCI, PHO5, TRPI, ADHI, ADH2, the genes for glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, triose phosphate isomerase, phosphoglucose isomerase, glucokinase, alpha-mating factor pheromone, [a mating factor pheromone], the PRBI promoter, the GUT2 promoter, the GPDI promoter, and hybrid promoters involving hybrids of parts of 5' regulatory regions with parts of 5' regulatory regions of other promoters or with upstream activation sites (*e.g.* the promoter of EP-A-258 067).

[0304] Convenient regulatable promoters for use in *Schizosaccharomyces pombe* are the thiamine-repressible promoter from the nmt gene as described by Maundrell (1990) *J. Biol. Chem.* 265, 10857-10864 and the glucose repressible jbpl gene promoter as described by Hoffman & Winston (1990) *Genetics* 124, 807-816.

[0305] Methods of transforming *Pichia* for expression of foreign genes are taught in, for example, Cregg *et al.* (1993), and various Phillips patents (*e.g.* US 4 857 467,

incorporated herein by reference), and *Pichia* expression kits are commercially available from Invitrogen BV, Leek, Netherlands, and Invitrogen Corp., San Diego, California. Suitable promoters include AOXI and AOX2. Gleeson *et al.* (1986) J. Gen. Microbiol. 132, 3459-3465 include information on *Hansenula* vectors and transformation, suitable promoters being MOX1 and FMD1; whilst EP 361 991, Fleer *et al.* (1991) and other-publications from Rhone-Poulenc Rorer teach how to express foreign proteins in *Kluyveromyces* spp., a suitable promoter being PGKI.

[0306] The transcription termination signal is preferably the 3' flanking sequence of a eukaryotic gene which contains proper signals for transcription termination and polyadenylation. Suitable 3' flanking sequences may, for example, be those of the gene naturally linked to the expression control sequence used, *i.e.*, may correspond to the promoter. Alternatively, they may be different in which case the termination signal of the S. cerevisiae ADHI gene is preferred.

[0307] The desired albumin fusion protein may be initially expressed with a secretion leader sequence, which may be any leader effective in the yeast chosen. Leaders useful in yeast include any of the following:

a) the MPIF-1 signal sequence (e.g., amino acids 1-21 of GenBank Accession number AAB51134) MKVSVAALSCLMLVTALGSQA (SEQ ID NO:825)

b) the stanniocalcin signal sequence (MLQNSAVLLLLVISASA, SEQ ID NO:340)

c) the pre-pro region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYSRGVFRR, SEQ ID NO:410)

d) the pre region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYS, SEQ ID NO:411) or variants thereof, such as, for example, MKWVSFISLLFLFSSAYS, (SEQ ID NO:408)

e) the invertase signal sequence (e.g., MLLQAFLFLLAGFAAKISA, SEQ ID NO:393)

f) the yeast mating factor alpha signal sequence (e.g., MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVA VLPFSNSTNNGLLFINTTIASIAAKEEGVSLEKR, SEQ ID NO:394 or MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVA

VLPFSNSTNNGLLFINTTIASIAAKEEGVSLDKR, SEQ ID NO:394)

g) *K. lactis* killer toxin leader sequence

h) a hybrid signal sequence (e.g., MKWVSFISLLFLFSSAYSRSLEKR, SEQ ID NO:395)

i) an HSA/MFα-1 hybrid signal sequence (also known as HSA/kex2) (e.g., MKWVSFISLLFLFSSAYSRSLDKR, SEQ ID NO:396)

j) a *K. lactis* killer/ MFα-1 fusion leader sequence (e.g., MNIFYIFLFLLSFVQGSLDKR, SEQ ID NO:409)

k) the Immunoglobulin Ig signal sequence (e.g., MGWSCIILFLVATATGVHS, SEQ ID NO:380)

l) the Fibulin B precursor signal sequence (e.g., MERAAPSRRVPLPLLLLGGLALLAAGVDA, SEQ ID NO:381)

m) the clusterin precursor signal sequence (e.g., MMKTLLLFVGLLLTWESGQVLG, SEQ ID NO:382)

n) the insulin-like growth factor-binding protein 4 signal sequence (e.g., MLPLCLVAALLLAAGPGPSLG, SEQ ID NO:383)

o) variants of the pre-pro-region of the HSA signal sequence such as, for example,

MKWVSFISLLFLFSSAYSRGVFRR (SEQ ID NO:407),

MKWVTFISLLFLFAGVLG (SEQ ID NO:384),

MKWVTFISLLFLFSGVLG (SEQ ID NO:385),

MKWVTFISLLFLFGGVLG (SEQ ID NO:386),

Modified HSA leader HSA #64

MKWVTFISLLFLFAGVSG (SEQ ID NO:826);

Modified HSA leader HSA #66

MKWVTFISLLFLFGGVSG (SEQ ID NO:827);

Modified HSA (A14) leader –

MKWVTFISLLFLFAGVSG (SEQ ID NO:387);

Modified HSA (S14) leader (also known as modified HSA #65) –

MKWVTFISLLFLFSGVSG (SEQ ID NO:388),

Modified HSA (G14) leader –

MKWVTFISLLFLFGGVSG (SEQ ID NO:389), or

MKWVTFISLLFLFGGVLGDLHKS (SEQ ID NO:390)

p) a consensus signal sequence (MPTWAWWLFLVLLLALWAPARG, SEQ ID NO:341)

q) acid phosphatase (PH05) leader (e.g., MFKSVVYSILAASLANA SEQ ID NO:828)

r) the pre-sequence of MFoz-1

s) the pre-sequence of 0 glucanase (BGL2)

t) killer toxin leader

u) the presequence of killer toxin

v) k. lactis killer toxin prepro (29 amino acids; 16 amino acids of pre and 13 amino acids of pro) MNIFYIFLFLLSFVQGLEHTHRRGSLDKR (SEQ ID NO:829)

w) *S. diastaticus* glucoarnylase II secretion leader sequence

x) *S. carlsbergensis* α-galactosidase (MEL1) secretion leader sequence

Candida glucoarnylase leader sequence

z) The hybrid leaders disclosed in EP-A-387 319 (herin incorporated by reference)

aa) the gp67 signal sequence (in conjunction with baculoviral expression systems) (e.g., amino acids 1-19 of GenBank Accession Number AAA72759) or

bb) the natural leader of the therapeutic protein X;

cc) S. cerevisiae invertase (SUC2) leader, as disclosed in JP 62-096086 (granted as 911036516, herein incorporate by reference); or

dd) Inulinase – MKLAYSLLLPLAGVSASVINYKR (SEQ ID NO:830).

ee) A modified TA57 propeptide leader variant #1 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNS GGLDVVGLISMAKR (SEQ ID NO:821)

ff) A modified TA57 propeptide leader variant #2 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNS GGLDVVGLISMAEEGEPKR (SEQ ID NO:822)

Additional Methods of Recombinant and Synthetic Production of Albumin Fusion Proteins

[0308] The present invention also relates to vectors containing a polynucleotide encoding an albumin fusion protein of the present invention, host cells, and the production of albumin fusion proteins by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0309] The polynucleotides encoding albumin fusion proteins of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

[0310] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac, trp, phoA* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0311] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli,* Streptomyces and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS,NSO, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0312] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9,

available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[0313] In one embodiment, polynucleotides encoding an albumin fusion protein of the invention may be fused to signal sequences which will direct the localization of a protein of the invention to particular compartments of a prokaryotic or eukaryotic cell and/or direct the secretion of a protein of the invention from a prokaryotic or eukaryotic cell. For example, in *E. coli*, one may wish to direct the expression of the protein to the periplasmic space. Examples of signal sequences or proteins (or fragments thereof) to which the albumin fusion proteins of the invention may be fused in order to direct the expression of the polypeptide to the periplasmic space of bacteria include, but are not limited to, the *pelB* signal sequence, the maltose binding protein (MBP) signal sequence, MBP, the *ompA* signal sequence, the signal sequence of the periplasmic *E. coli* heat-labile enterotoxin B-subunit, and the signal sequence of alkaline phosphatase. Several vectors are commercially available for the construction of fusion proteins which will direct the localization of a protein, such as the pMAL series of vectors (particularly the pMAL-p series) available from New England Biolabs. In a specific embodiment, polynucleotides albumin fusion proteins of the invention may be fused to the *pelB* pectate lyase signal sequence to increase the efficiency of expression and purification of such polypeptides in Gram-negative bacteria. *See*, U.S. Patent Nos. 5,576,195 and 5,846,818, the contents of which are herein incorporated by reference in their entireties.

[0314] Examples of signal peptides that may be fused to an albumin fusion protein of the invention in order to direct its secretion in mammalian cells include, but are not limited to:

a) the MPIF-1 signal sequence (e.g., amino acids 1-21 of GenBank Accession

number AAB51134) MKVSVAALSCLMLVTALGSQA (SEQ ID NO:825)

b) the stanniocalcin signal sequence (MLQNSAVLLLLVISASA, SEQ ID NO:340)

c) the pre-pro region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYSRGVFRR, SEQ ID NO:410)

d) the pre region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYS, SEQ ID NO:411) or variants thereof, such as, for example, MKWVSFISLLFLFSSAYS, (SEQ ID NO:408)

e) the invertase signal sequence (e.g., MLLQAFLFLLAGFAAKISA, SEQ ID NO:393)

f) the yeast mating factor alpha signal sequence (e.g., MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVA VLPFSNSTNNGLLFINTTIASIAAKEEGVSLEKR, SEQ ID NO:394 or MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVA VLPFSNSTNNGLLFINTTIASIAAKEEGVSLDKR, SEQ ID NO:394)

g) *K. lactis* killer toxin leader sequence

h) a hybrid signal sequence (e.g., MKWVSFISLLFLFSSAYSRSLEKR, SEQ ID NO:395)

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MKWVTFISLLFLFSGVSG (SEQ ID NO:388),

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p) a consensus signal sequence (MPTWAWWLFLVLLLALWAPARG, SEQ ID NO:341)

q) acid phosphatase (PH05) leader (e.g., MFKSVVYSILAASLANA SEQ ID NO:828)

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w) *S. diastaticus* glucoamylase II secretion leader sequence

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Candida glucoamylase leader sequence

z) The hybrid leaders disclosed in EP-A-387 319 (herin incorporated by reference)

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(e.g., amino acids 1-19 of GenBank Accession Number AAA72759) or

bb) the natural leader of the therapeutic protein X;

cc) S. cerevisiae invertase (SUC2) leader, as disclosed in JP 62-096086 (granted as 911036516, herein incorporate by reference); or

dd) Inulinase – MKLAYSLLLPLAGVSASVINYKR (SEQ ID NO:830).

ee) A modified TA57 propeptide leader variant #1 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNS GGLDVVGLISMAKR (SEQ ID NO:821)

ff) A modified TA57 propeptide leader variant #2 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNS GGLDVVGLISMAEEGEPKR (SEQ ID NO:822)

[0315] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NSO) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

[0316] The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a

human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[0317] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[0318] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence corresponding to a Therapeutic protein may be replaced with an albumin fusion protein corresponding to the Therapeutic protein), and/or to include genetic material (e.g., heterologous polynucleotide sequences such as for example, an albumin fusion protein of the invention corresponding to the Therapeutic protein may be included). The genetic material operably associated with the endogenous polynucleotide may activate, alter, and/or amplify endogenous polynucleotides.

[0319] In addition, techniques known in the art may be used to operably associate heterologous polynucleotides (e.g., polynucleotides encoding an albumin protein, or a fragment or variant thereof) and/or heterologous control regions (e.g., promoter and/or enhancer) with endogenous polynucleotide sequences encoding a Therapeutic protein via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997;

International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al., Proc. Natl. Acad. Sci. USA 86*:8932-8935 (1989); and Zijlstra *et al., Nature 342*:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0320] Albumin fusion proteins of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, hydrophobic charge interaction chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

[0321] In preferred embodiments the albumin fusion proteins of the invention are purified using Anion Exchange Chromatography including, but not limited to, chromatography on Q-sepharose, DEAE sepharose, poros HQ, poros DEAE, Toyopearl Q, Toyopearl QAE, Toyopearl DEAE, Resource/Source Q and DEAE, Fractogel Q and DEAE columns.

[0322] In specific embodiments the albumin fusion proteins of the invention are purified using Cation Exchange Chromatography including, but not limited to, SP-sepharose, CM sepharose, poros HS, poros CM, Toyopearl SP, Toyopearl CM, Resource/Source S and CM, Fractogel S and CM columns and their equivalents and comparables.

[0323] In specific embodiments the albumin fusion proteins of the invention are purified using Hydrophobic Interaction Chromatography including, but not limited to, Phenyl, Butyl, Methyl, Octyl, Hexyl-sepharose, poros Phenyl, Butyl, Methyl, Octyl, Hexyl , Toyopearl Phenyl, Butyl, Methyl, Octyl, Hexyl Resource/Source Phenyl, Butyl, Methyl, Octyl, Hexyl, Fractogel Phenyl, Butyl, Methyl, Octyl, Hexyl columns and their equivalents and comparables.

[0324] In specific embodiments the albumin fusion proteins of the invention are purified using Size Exclusion Chromatography including, but not limited to, sepharose S100, S200, S300, superdex resin columns and their equivalents and comparables.

[0325] In specific embodiments the albumin fusion proteins of the invention are

purified using Affinity Chromatography including, but not limited to, Mimetic Dye affinity, peptide affinity and antibody affinity columns that are selective for either the HSA or the "fusion target" molecules.

[0326] In preferred embodiments albumin fusion proteins of the invention are purified using one or more Chromatography methods listed above. In other preferred embodiments, albumin fusion proteins of the invention are purified using one or more of the following Chromatography columns, Q sepharose FF column, SP Sepharose FF column, Q Sepharose High Performance Column, Blue Sepharose FF column, Blue Column, Phenyl Sepharose FF column, DEAE Sepharose FF, or Methyl Column.

[0327] Additionally, albumin fusion proteins of the invention may be purified using the process described in PCT International Publication WO 00/44772 which is herein incorporated by reference in its entirety. One of skill in the art could easily modify the process described therein for use in the purification of albumin fusion proteins of the invention.

[0328] Albumin fusion proteins of the present invention may be recovered from: products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, albumin fusion proteins of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0329] In one embodiment, the yeast *Pichia pastoris* is used to express albumin fusion proteins of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This

reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See Ellis, S.B., *et al., Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al., Yeast* 5:167-77 (1989); Tschopp, J.F., *et al., Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[0330] In one example, the plasmid vector pPIC9K is used to express DNA encoding an albumin fusion protein of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[0331] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0332] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide encoding an albumin fusion protein of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[0333] In a preferred embodiment, an albumin fusion protein of the invention is processed by a host cell and secreted into the surrounding culture medium. Processing of the nascent albumin fusion protein that occurs in the secretory pathways of the host used for expression may include, but is not limited to signal peptide cleavage; formation of disulfide bonds; proper folding; addition and processing of carbohydrates (such as for example, N- and O- linked glycosylation); specific proteolytic cleavages; and assembly into multimeric proteins. An albumin fusion protein of the invention is preferably in the processed form. In a most preferred embodiment, the "processed form of an albumin fusion protein" refers to an albumin fusion protein product which has undergone N-terminal signal peptide cleavage, herein also referred to as a "mature albumin fusion protein".

[0334] In addition, albumin fusion proteins of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0335] The invention encompasses albumin fusion proteins of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques,

including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[0336] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The albumin fusion proteins may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0337] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (^{121}I, ^{123}I, ^{125}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{111}In, ^{112}In, ^{113m}In, ^{115m}In), technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, and ^{97}Ru.

[0338] In specific embodiments, albumin fusion proteins of the present invention or fragments or variants thereof are attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, ^{177}Lu, ^{90}Y, ^{166}Ho, and ^{153}Sm, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is ^{111}In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is ^{90}Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via linker molecule. Examples of linker molecules useful for conjugating DOTA to a

polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[0339] As mentioned, the albumin fusion proteins of the invention may be modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POST-TRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0340] Albumin fusion proteins of the invention and antibodies that bind a Therapeutic protein or fragments or variants thereof can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are

commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[0341] Further, an albumin fusion protein of the invention may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0342] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol.,*

6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors. Techniques for conjugating such therapeutic moiety to proteins (e.g., albumin fusion proteins) are well known in the art.

[0343] Albumin fusion proteins may also be attached to solid supports, which are particularly useful for immunoassays or purification of polypeptides that are bound by, that bind to, or associate with albumin fusion proteins of the invention. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0344] Albumin fusion proteins, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

[0345] In embodiments where the albumin fusion protein of the invention comprises only the VH domain of an antibody that binds a Therapeutic protein, it may be necessary and/or desirable to coexpress the fusion protein with the VL domain of the same antibody that binds a Therapeutic protein, such that the VH-albumin fusion protein and VL protein will associate (either covalently or non-covalently) post-translationally.

[0346] In embodiments where the albumin fusion protein of the invention comprises only the VL domain of an antibody that binds a Therapeutic protein, it may be necessary and/or desirable to coexpress the fusion protein with the VH domain of the same antibody that binds a Therapeutic protein, such that the VL-albumin fusion protein and VH protein will associate (either covalently or non-covalently) post-translationally.

[0347] Some Therapeutic antibodies are bispecific antibodies, meaning the antibody that binds a Therapeutic protein is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. In order to create an albumin fusion protein corresponding to that Therapeutic protein, it is possible to create an albumin fusion protein which has an scFv fragment fused to both the N- and C- terminus of the albumin protein moiety. More particularly, the scFv fused to the N-terminus of albumin

would correspond to one of the heavy/light (VH/VL) pairs of the original antibody that binds a Therapeutic protein and the scFv fused to the C-terminus of albumin would correspond to the other heavy/light (VH/VL) pair of the original antibody that binds a Therapeutic protein.

[0348] Also provided by the invention are chemically modified derivatives of the albumin fusion proteins of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The albumin fusion proteins may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0349] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a Therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0350] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al., Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al., Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al., Bioconjug. Chem.*

10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0351] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0352] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0353] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a

population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0354] As indicated above, pegylation of the albumin fusion proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the albumin fusion protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0355] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

[0356] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire

disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0357] The number of polyethylene glycol moieties attached to each albumin fusion protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

[0358] The polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[0359] The presence and quantity of albumin fusion proteins of the invention may be determined using ELISA, a well known immunoassay known in the art. In one ELISA protocol that would be useful for detecting/quantifying albumin fusion proteins of the invention, comprises the steps of coating an ELISA plate with an anti-human serum albumin antibody, blocking the plate to prevent non-specific binding, washing the ELISA plate, adding a solution containing the albumin fusion protein of the invention (at one or more different concentrations), adding a secondary anti-Therapeutic protein specific antibody coupled to a detectable label (as described herein or otherwise known in the art), and detecting the presence of the secondary antibody. In an alternate version of this protocol, the ELISA plate might be coated with the anti-Therapeutic protein specific antibody and the labeled secondary reagent might be the anti-human albumin specific

antibody.

Uses of the Polynucleotides

[0360] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[0361] The polynucleotides of the present invention are useful to produce the albumin fusion proteins of the invention. As described in more detail below, polynucleotides of the invention (encoding albumin fusion proteins) may be used in recombinant DNA methods useful in genetic engineering to make cells, cell lines, or tissues that express the albumin fusion protein encoded by the polynucleotides encoding albumin fusion proteins of the invention.

[0362] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy", and Examples 47 and 48).

Uses of the Polypeptides

[0363] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0364] Albumin fusion proteins of the invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0365] Albumin fusion proteins can be used to assay levels of polypeptides in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell.

Biol. 105:3087-3096 (1987)). Other methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0366] Albumin fusion proteins of the invention can also be detected *in vivo* by imaging. Labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, nuclear magnetic resonance (NMR) or electron spin relaxtion (ESR). For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the albumin fusion protein by labeling of nutrients given to a cell line expressing the albumin fusion protein of the invention.

[0367] An albumin fusion protein which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc, (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F, ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled albumin fusion protein will then preferentially accumulate at locations in the body (e.g., organs, cells, extracellular spaces or matrices) where one or more receptors, ligands

or substrates (corresponding to that of the Therapeutic protein used to make the albumin fusion protein of the invention) are located. Alternatively, in the case where the albumin fusion protein comprises at least a fragment or variant of a Therapeutic antibody, the labeled albumin fusion protein will then preferentially accumulate at the locations in the body (e.g., organs, cells, extracellular spaces or matrices) where the polypeptides/epitopes corresponding to those bound by the Therapeutic antibody (used to make the albumin fusion protein of the invention) are located. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)). The protocols described therein could easily be modified by one of skill in the art for use with the albumin fusion proteins of the invention.

[0368] In one embodiment, the invention provides a method for the specific delivery of albumin fusion proteins of the invention to cells by administering albumin fusion proteins of the invention (e.g., polypeptides encoded by polynucleotides encoding albumin fusion proteins of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a Therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0369] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering albumin fusion proteins of the invention in association with toxins or cytotoxic prodrugs.

[0370] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine

kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{90}Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{111}In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{131}I.

[0371] Techniques known in the art may be applied to label polypeptides of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0372] The albumin fusion proteins of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described in column 4 of Table 1 corresponding to a Therapeutic protein of interest, and/or as described under the section heading "Biological Activities," below.

[0373] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a certain polypeptide in cells or body fluid of an individual using an albumin fusion protein of the invention; and (b) comparing the assayed

polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0374] Moreover, albumin fusion proteins of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0375] In particular, albumin fusion proteins comprising of at least a fragment or variant of a Therapeutic antibody can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an albumin fusion protein comprising of at least a fragment or variant of a Therapeutic antibody can bind, and/or neutralize the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein specifically binds, and/or reduce overproduction of the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein specifically binds. Similarly, administration of an albumin fusion protein comprising of at least a fragment or variant of a Therapeutic antibody can activate the polypeptide to which the Therapeutic

antibody used to make the albumin fusion protein specifically binds, by binding to the polypeptide bound to a membrane (receptor).

[0376] At the very least, the albumin fusion proteins of the invention of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Albumin fusion proteins of the invention can also be used to raise antibodies, which in turn may be used to measure protein expression of the Therapeutic protein, albumin protein, and/or the albumin fusion protein of the invention from a recombinant cell, as a way of assessing transformation of the host cell, or in a biological sample. Moreover, the albumin fusion proteins of the present invention can be used to test the biological activities described herein.

Diagnostic Assays

[0377] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described for each Therapeutic protein in the corresponding row of Table 1 and herein under the section headings "Immune Activity," "Blood Related Disorders," "Hyperproliferative Disorders," "Renal Disorders," "Cardiovascular Disorders," "Respiratory Disorders," "Anti-Angiogenesis Activity," "Diseases at the Cellular Level," "Wound Healing and Epithelial Cell Proliferation," "Neural Activity and Neurological Diseases," "Endocrine Disorders," "Reproductive System Disorders," "Infectious Disease," "Regeneration," and/or "Gastrointestinal Disorders," *infra.*

[0378] For a number of disorders, substantially altered (increased or decreased) levels of gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding a polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a

standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

[0379] The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed gene expression will experience a worse clinical outcome.

[0380] By "assaying the expression level of the gene encoding a polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of a particular polypeptide (e.g. a polypeptide corresponding to a Therapeutic protein disclosed in Table 1) or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0381] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0382] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate

method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[0383] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides that bind to, are bound by, or associate with albumin fusion proteins of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting abnormal expression of polypeptides that bind to, are bound by, or associate with albumin fusion proteins compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide that bind to, are bound by, or associate with albumin fusion proteins of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

[0384] Assaying polypeptide levels in a biological sample can occur using a variety of techniques. For example, polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987)). Other methods useful for detecting polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0385] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of interest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual",

Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

[0386] For example, albumin fusion proteins may be used to quantitatively or qualitatively detect the presence of polypeptides that bind to, are bound by, or associate with albumin fusion proteins of the present invention. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled albumin fusion protein coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0387] In a preferred embodiment, albumin fusion proteins comprising at least a fragment or variant of an antibody that specifically binds at least a Therapeutic protein disclosed herein (e.g., the Therapeutic proteins disclosed in Table 1) or otherwise known in the art may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0388] The albumin fusion proteins of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of polypeptides that bind to, are bound by, or associate with an albumin fusion protein of the present invention. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The albumin fusion proteins are preferably applied by overlaying the labeled albumin fusion proteins onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the polypeptides that bind to, are bound by, or associate with albumin fusion proteins, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0389] Immunoassays and non-immunoassays that detect polypeptides that bind to, are

bound by, or associate with albumin fusion proteins will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[0390] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled albumin fusion protein of the invention. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[0391] By "solid phase support or carrier" is intended any support capable of binding a polypeptide (e.g., an albumin fusion protein, or polypeptide that binds, is bound by, or associates with an albumin fusion protein of the invention.) Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to a polypeptide. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0392] The binding activity of a given lot of albumin fusion protein may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[0393] In addition to assaying polypeptide levels in a biological sample obtained from an individual, polypeptide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, albumin fusion proteins of the invention are used to image diseased or neoplastic cells.

[0394] Labels or markers for *in vivo* imaging of albumin fusion proteins of the invention include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the albumin fusion protein by labeling of nutrients of a cell line (or bacterial or yeast strain) engineered.

[0395] Additionally, albumin fusion proteins of the invention whose presence can be detected, can be administered. For example, albumin fusion proteins of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for *in vitro* diagnostic procedures.

[0396] A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled albumin fusion protein will then preferentially accumulate at the locations in the body which contain a polypeptide or other substance that binds to, is bound by or associates with an albumin fusion protein of the present invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0397] One of the ways in which an albumin fusion protein of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0398] Albumin fusion proteins may also be radiolabeled and used in any of a variety of other immunoassays. For example, by radioactively labeling the albumin fusion proteins, it is possible to the use the albumin fusion proteins in a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[0399] Additionally, chelator molecules, are known in the art and can be used to label the Albumin fusion proteins. Chelator molecules may be attached Albumin fusion proteins of the invention to facilitate labeling said protein with metal ions including radionuclides or fluorescent labels. For example, see Subramanian, R. and Meares, C.F.,

"Bifunctional Chelating Agents for Radiometal-labeled monoclonal Antibodies," in *Cancer Imaging with Radiolabeled Antibodies* (D. M. Goldenberg, Ed.) Kluwer Academic Publications, Boston; Saji, H., "Targeted delivery of radiolabeled imaging and therapeutic agents: bifunctional radiopharmaceuticals." *Crit. Rev. Ther. Drug Carrier Syst. 16*:209-244 (1999); Srivastava S.C. and Mease R.C., "Progress in research on ligands, nuclides and techniques for labeling monoclonal antibodies." *Int. J. Rad. Appl. Instrum. B 18*:589-603 (1991); and Liu, S. and Edwards, D.S., "Bifunctional chelators for therapeutic lanthanide radiopharmaceuticals." *Bioconjug. Chem. 12*:7-34 (2001). Any chelator which can be covalently bound to said Albumin fusion proteins may be used according to the present invention. The chelator may further comprise a linker moiety that connects the chelating moiety to the Albumin fusion protein.

[0400] In one embodiment, the Albumin fusion protein of the invention are attached to an acyclic chelator such as diethylene triamine-N,N,N',N";N"-pentaacetic acid (DPTA), analogues of DPTA, and derivatives of DPTA. As non-limiting examples, the chelator may be 2-(p-isothiocyanatobenzyl)-6- methyldiethylenetriaminepentaacetic acid (1B4M-DPTA, also known as MX-DTPA), 2-methyl-6-(rho-nitrobenzyl)-1,4,7- triazaheptane-N,N,N',N",N"-pentaacetic acid (nitro-1B4M-DTPA or nitro-MX-DTPA); 2-(p-isothiocyanatobenzyl)-cyclohexyldiethylenetriaminepentaacetic acid (CHX-DTPA), or N-[2-amino-3-(rho-nitrophenyl)propyl]-trans-cyclohexane-1,2-diamine-N,N',N"-pentaacetic acid (nitro-CHX-A-DTPA). In another embodiment, the Albumin fusion protein of the invention are attached to an acyclic terpyridine chelator such as 6,6"-bis[[N,N,N",N"-tetra(carboxymethyl)amino]methyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2 "- terpyridine (TMT-amine).

[0401] In specific embodiments, the macrocyclic chelator which is attached to the the Albumin fusion protein of the invention is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the the Albumin fusion protein of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo *et al.*, *Clin. Cancer Res. 4*(10):2483-90, 1998; Peterson *et al.*, *Bioconjug. Chem. 10*(4):553-7, 1999; and Zimmerman *et al.*, *Nucl. Med. Biol. 26*(8):943-50, 1999 which are hereby incorporated by reference in their entirety. In addition, U.S.

Patents 5,652,361 and 5,756,065, which disclose chelating agents that may be conjugated to antibodies, and methods for making and using them, are hereby incorporated by reference in their entireties. Though U.S. Patents 5,652,361 and 5,756,065 focus on conjugating chelating agents to antibodies, one skilled in the art could readily adapt the method disclosed therein in order to conjugate chelating agents to other polypeptides.

[0402] Bifunctional chelators based on macrocyclic ligands in which conjugation is via an activated arm, or functional group, attached to the carbon backbone of the ligand can be employed as described by M. Moi *et al.*, *J. Amer. Chem. Soc. 49*:2639 (1989) (2-*p*-nitrobenzyl-1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid); S. V. Deshpande *et al.*, *J. Nucl. Med. 31*:473 (1990); G. Ruser *et al.*, *Bioconj. Chem. 1*:345 (1990); C. J. Broan *et al.*, *J. C. S. Chem. Comm. 23*:1739 (1990); and C. J. Anderson *et al.*, *J. Nucl. Med. 36*:850 (1995).

[0403] In one embodiment, a macrocyclic chelator, such as polyazamacrocyclic chelators, optionally containing one or more carboxy, amino, hydroxamate, phosphonate, or phosphate groups, are attached to the Albumin fusion protein of the invention. In another embodiment, the chelator is a chelator selected from the group consisting of DOTA, analogues of DOTA, and derivatives of DOTA.

[0404] In one embodiment, suitable chelator molecules that may be attached to the the Albumin fusion protein of the invention include DOXA (1-oxa-4,7,10-triazacyclododecanetriacetic acid), NOTA (1,4,7-triazacyclononanetriacetic acid), TETA (1,4,8,11-tetraazacyclotetradecanetetraacetic acid), and THT (4'-(3-amino-4-methoxy-phenyl)-6,6"-bis(N',N'-dicarboxymethyl-*N*-methylhydra zino)-2,2':6',2"-terpyridine), and analogs and derivatives thereof. See, *e.g.*, Ohmono *et al.*, *J. Med. Chem. 35*: 157-162 (1992); Kung *et al.*, *J. Nucl. Med. 25*: 326-332 (1984); Jurisson *et al.*, *Chem. Rev. 93*:1137-1156 (1993); and U.S. Patent No. 5,367,080. Other suitable chelators include chelating agents disclosed in U.S. Patent Nos. 4,647,447; 4,687,659; 4,885,363; EP-A-71564; WO89/00557; and EP-A-232751.

[0405] In another embodiment, suitable macrocyclic carboxylic acid chelators which can be used in the present invention include 1,4,7,10-tetraazacyclododecane-*N,N',N",N"'*-tetraacetic acid (DOTA); 1,4,8,12-tetraazacyclopentadecane-*N,N',N",N"'*-tetraacetic acid (15N4); 1,4,7-triazacyclononane-N,N',N"-triacetic acid (9N3); 1,5,9-triazacyclododecane-

N,N',N"-triacetic acid (12N3); and 6-bromoacetamido-benzyl-1;4,8,11-tetraazacyclotetradecane- *N,N',N",N"'*-tetraacetic acid (BAT).

[0406] A preferred chelator that can be attached to the Albumin Fusion protein of the invention is α-(5-isothiocyanato- 2-methoxyphenyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, which is also known as MeO-DOTA-NCS. A salt or ester of α-(5-isothiocyanato- 2-methoxyphenyl)- 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid may also be used.

[0407] Albumin fusion proteins of the invention to which chelators such as those decribed are covalently attached may be labeled (via the coordination site of the chelator) with radionuclides that are suitable for therapeutic, diagnostic, or both therapeutic and diagnostic purposes. Examples of appropriate metals include Ag, At, Au, Bi, Cu, Ga, Ho, In, Lu, Pb, Pd, Pm, Pr, Rb, Re, Rh, Sc, Sr, Tc, Tl, Y, and Yb. Examples of the radionuclide used for diagnostic purposes are Fe, Gd, ^{111}In, ^{67}Ga, or ^{68}Ga. In another embodiment, the radionuclide used for diagnostic purposes is ^{111}In, or ^{67}Ga. Examples of the radionuclide used for therapeutic purposes are ^{166}Ho, ^{165}Dy, ^{90}Y, ^{115m}In, ^{52}Fe, or ^{72}Ga. In one embodiment, the radionuclide used for diagnostic purposes is ^{166}Ho or ^{90}Y. Examples of the radionuclides used for both therapeutic and diagnostic purposes include ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{175}Yb, or ^{47}Sc. In one embodiment, the radionuclide is ^{153}Sm, ^{177}Lu, ^{175}Yb, or ^{159}Gd.

[0408] Preferred metal radionuclides include ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{95}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{203}Pb and ^{141}Ce.

[0409] In a particular embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with a metal ion selected from the group consisting of ^{90}Y, ^{111}In, ^{177}Lu, ^{166}Ho, ^{215}Bi, and ^{225}Ac.

[0410] Moreover, γ-emitting radionuclides, such as ^{99m}Tc, ^{111}In, ^{67}Ga, and ^{169}Yb have been approved or under investigation for diagnostic imaging, while β-emitters, such as ^{67}Cu, ^{111}Ag, ^{186}Re, and ^{90}Y are useful for the applications in tumor therapy. Also other useful radionuclides include γ-emitters, such as ^{99m}Tc, ^{111}In, ^{67}Ga, and ^{169}Yb, and β-emitters, such as ^{67}Cu, ^{111}Ag, ^{186}Re, ^{188}Re and ^{90}Y, as well as other radionuclides of interest such as ^{211}At, ^{212}Bi, ^{177}Lu, ^{86}Rb , ^{105}Rh, ^{153}Sm, ^{198}Au, ^{149}Pm, ^{85}Sr, ^{142}Pr, ^{214}Pb,

^{109}Pd, ^{166}Ho, ^{208}Tl, and ^{44}Sc. Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with the radionuclides described above.

[0411] In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with paramagnetic metal ions including ions of transition and lanthanide metal, such as metals having atomic numbers of 21-29, 42, 43, 44, or 57-71, in particular ions of Cr, V, Mn, Fe, Co, Ni, Cu, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu. The paramagnetic metals used in compositions for magnetic resonance imaging include the elements having atomic numbers of 22 to 29, 42, 44 and 58-70.

[0412] In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with fluorescent metal ions including lanthanides, in particular La, Ce, Pr, Nd, Pm, Sm, Eu (e.g., ^{152}Eu), Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu.

[0413] In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with heavy metal-containing reporters may include atoms of Mo, Bi, Si, and W.

[0414] It is also possible to label the albumin fusion proteins with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[0415] The albumin fusion protein can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0416] The albumin fusion proteins can also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged albumin fusion protein is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium

ester, imidazole, acridinium salt and oxalate ester.

[0417] Likewise, a bioluminescent compound may be used to label albumin fusion proteins of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Transgenic Organisms

[0418] Transgenic organisms that express the albumin fusion proteins of the invention are also included in the invention. Transgenic organisms are genetically modified organisms into which recombinant, exogenous or cloned genetic material has been transferred. Such genetic material is often referred to as a transgene. The nucleic acid sequence of the transgene may include one or more transcriptional regulatory sequences and other nucleic acid sequences such as introns, that may be necessary for optimal expression and secretion of the encoded protein. The transgene may be designed to direct the expression of the encoded protein in a manner that facilitates its recovery from the organism or from a product produced by the organism, *e.g.* from the milk, blood, urine, eggs, hair or seeds of the organism. The transgene may consist of nucleic acid sequences derived from the genome of the same species or of a different species than the species of the target animal. The transgene may be integrated either at a locus of a genome where that particular nucleic acid sequence is not otherwise normally found or at the normal locus for the transgene.

[0419] The term "germ cell line transgenic organism" refers to a transgenic organism in which the genetic alteration or genetic information was introduced into a germ line cell, thereby conferring the ability of the transgenic organism to transfer the genetic information to offspring. If such offspring in fact possess some or all of that alteration or genetic information, then they too are transgenic organisms. The alteration or genetic information may be foreign to the species of organism to which the recipient belongs, foreign only to the particular individual recipient, or may be genetic information already possessed by the recipient. In the last case, the altered or introduced gene may be expressed differently than

the native gene.

[0420] A transgenic organism may be a transgenic animal or a transgenic plant. Transgenic animals can be produced by a variety of different methods including transfection, electroporation, microinjection, gene targeting in embryonic stem cells and recombinant viral and retroviral infection (*see, e.g.*, U.S. Patent No. 4,736,866; U.S. Patent No. 5,602,307; Mullins *et al.* (1993) Hypertension 22(4):630-633; Brenin *et al.* (1997) Surg. Oncol. 6(2)99-110; Tuan (ed.), *Recombinant Gene Expression Protocols*, Methods in Molecular Biology No. 62, Humana Press (1997)). The method of introduction of nucleic acid fragments into recombination competent mammalian cells can be by any method which favors co-transformation of multiple nucleic acid molecules. Detailed procedures for producing transgenic animals are readily available to one skilled in the art, including the disclosures in U.S. Patent No. 5,489,743 and U.S. Patent No. 5,602,307.

[0421] A number of recombinant or transgenic mice have been produced, including those which express an activated oncogene sequence (U.S. Patent No. 4,736,866); express simian SV40 T-antigen (U.S. Patent No. 5,728,915); lack the expression of interferon regulatory factor 1 (IRF-1) (U.S. Patent No. 5,731,490); exhibit dopaminergic dysfunction (U.S. Patent No. 5,723,719); express at least one human gene which participates in blood pressure control (U.S. Patent No. 5,731,489); display greater similarity to the conditions existing in naturally occurring Alzheimer's disease (U.S. Patent No. 5,720,936); have a reduced capacity to mediate cellular adhesion (U.S. Patent No. 5,602,307); possess a bovine growth hormone gene (Clutter *et al.* (1996) Genetics 143(4):1753-1760); or, are capable of generating a fully human antibody response (McCarthy (1997) The Lancet 349(9049):405).

[0422] While mice and rats remain the animals of choice for most transgenic experimentation, in some instances it is preferable or even necessary to use alternative animal species. Transgenic procedures have been successfully utilized in a variety of non-murine animals, including sheep, goats, pigs, dogs, cats, monkeys, chimpanzees, hamsters, rabbits, cows and guinea pigs (*see, e.g.*, Kim *et al.* (1997) Mol. Reprod. Dev. 46(4):515-526; Houdebine (1995) Reprod. Nutr. Dev. 35(6):609-617; Petters (1994) Reprod. Fertil. Dev. 6(5):643-645; Schnieke *et al.* (1997) Science 278(5346):2130-2133; and Amoah

(1997) J. Animal Science 75(2):578-585).

[0423] To direct the secretion of the transgene-encoded protein of the invention into the milk of transgenic mammals, it may be put under the control of a promoter that is preferentially activated in mammary epithelial cells. Promoters that control the genes encoding milk proteins are preferred, for example the promoter for casein, beta lactoglobulin, whey acid protein, or lactalbumin (see, *e.g.*, DiTullio (1992) BioTechnology 10:74-77; Clark *et al.* (1989) BioTechnology 7:487-492; Gorton *et al.* (1987) BioTechnology 5:1183-1187; and Soulier *et al.* (1992) FEBS Letts. 297:13). The transgenic mammals of choice would produce large volumes of milk and have long lactating periods, for example goats, cows, camels or sheep.

[0424] An albumin fusion protein of the invention can also be expressed in a transgenic plant, *e.g.* a plant in which the DNA transgene is inserted into the nuclear or plastidic genome. Plant transformation procedures used to introduce foreign nucleic acids into plant cells or protoplasts are known in the art. See, in general, Methods in Enzymology Vol. 153 ("Recombinant DNA Part D") 1987, Wu and Grossman Eds., Academic Press and European Patent Application EP 693554. Methods for generation of genetically engineered plants are further described in US Patent No. 5,283,184, US Patent No. 5, 482,852, and European Patent Application EP 693 554, all of which are hereby incorporated by reference.

Pharmaceutical or Therapeutic Compositions

[0425] The albumin fusion proteins of the invention or formulations thereof may be administered by any conventional method including parenteral (*e.g.* subcutaneous or intramuscular) injection or intravenous infusion. The treatment may consist of a single dose or a plurality of doses over a period of time.

[0426] While it is possible for an albumin fusion protein of the invention to be administered alone, it is preferable to present it as a pharmaceutical formulation, together with one or more acceptable carriers. The carrier(s) must be "acceptable" in the sense of being compatible with the albumin fusion protein and not deleterious to the recipients thereof. Typically, the carriers will be water or saline which will be sterile and pyrogen free. Albumin fusion proteins of the invention are particularly well suited to formulation

in aqueous carriers such as sterile pyrogen free water, saline or other isotonic solutions because of their extended shelf-life in solution. For instance, pharmaceutical compositions of the invention may be formulated well in advance in aqueous form, for instance, weeks or months or longer time periods before being dispensed.

[0427] In instances where aerosol administration is appropriate, the albumin fusion proteins of the invention can be formulated as aerosols using standard procedures. The term "aerosol" includes any gas-borne suspended phase of an albumin fusion protein of the instant invention which is capable of being inhaled into the bronchioles or nasal passages. Specifically, aerosol includes a gas-borne suspension of droplets of an albumin fusion protein of the instant invention, as may be produced in a metered dose inhaler or nebulizer, or in a mist sprayer. Aerosol also includes a dry powder composition of a compound of the instant invention suspended in air or other carrier gas, which may be delivered by insufflation from an inhaler device, for example. See Ganderton & Jones, *Drug Delivery to the Respiratory Tract, Ellis Horwood* (19 87); Gonda (1990) *Critical Reviews in Therapeutic Drug Carrier Systems* 6:273-313; and Raeburn *et al,.* (1992) *Pharmacol. Toxicol. Methods* 27:143-159.

[0428] The formulations of the invention are also typically non-immunogenic, in part, because of the use of the components of the albumin fusion protein being derived from the proper species. For instance, for human use, both the Therapeutic protein and albumin portions of the albumin fusion protein will typically be human. In some cases, wherein either component is non human-derived, that component may be humanized by substitution of key amino acids so that specific epitopes appear to the human immune system to be human in nature rather than foreign.

[0429] The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the albumin fusion protein with the carrier that constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0430] Formulations suitable for parenteral administration include aqueous and

non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation appropriate for the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules, vials or syringes, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders. Dosage formulations may contain the Therapeutic protein portion at a lower molar concentration or lower dosage compared to the non-fused standard formulation for the Therapeutic protein given the extended serum half-life exhibited by many of the albumin fusion proteins of the invention.

[0431] As an example, when an albumin fusion protein of the invention comprises growth hormone as one or more of the Therapeutic protein regions, the dosage form can be calculated on the basis of the potency of the albumin fusion protein relative to the potency of hGH, while taking into account the prolonged serum half-life and shelf-life of the albumin fusion proteins compared to that of native hGH. Growth hormone is typically administered at 0.3 to 30.0 IU/kg/week, for example 0.9 to 12.0 IU/kg/week, given in three or seven divided doses for a year or more. In an albumin fusion protein consisting of full length HA fused to full length GH, an equivalent dose in terms of units would represent a greater weight of agent but the dosage frequency can be reduced, for example to twice a week, once a week or less.

[0432] Formulations or compositions of the invention may be packaged together with, or included in a kit with, instructions or a package insert referring to the extended shelf-life of the albumin fusion protein component. For instance, such instructions or package inserts may address recommended storage conditions, such as time, temperature and light, taking into account the extended or prolonged shelf-life of the albumin fusion proteins of the invention. Such instructions or package inserts may also address the particular advantages of the albumin fusion proteins of the inventions, such as the ease of storage for formulations that may require use in the field, outside of controlled hospital, clinic or office conditions. As described above, formulations of the invention may be in aqueous

form and may be stored under less than ideal circumstances without significant loss of therapeutic activity.

[0433] Albumin fusion proteins of the invention can also be included in nutraceuticals. For instance, certain albumin fusion proteins of the invention may be administered in natural products, including milk or milk product obtained from a transgenic mammal which expresses albumin fusion protein. Such compositions can also include plant or plant products obtained from a transgenic plant which expresses the albumin fusion protein. The albumin fusion protein can also be provided in powder or tablet form, with or without other known additives, carriers, fillers and diluents. Nutraceuticals are described in Scott Hegenhart, *Food Product Design*, Dec. 1993.

[0434] The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of an albumin fusion protein of the invention or a polynucleotide encoding an albumin fusion protein of the invention ("albumin fusion polynucleotide") in a pharmaceutically acceptable carrier.

[0435] The albumin fusion protein and/or polynucleotide will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the albumin fusion protein and/or polynucleotide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[0436] As a general proposition, the total pharmaceutically effective amount of the albumin fusion protein administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the albumin fusion protein is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the

desired effect.

[0437] Albumin fusion proteins and/or polynucleotides can be are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[0438] Albumin fusion proteins and/or polynucleotides of the invention are also suitably administered by sustained-release systems. Examples of sustained-release albumin fusion proteins and/or polynucleotides are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion. Additional examples of sustained-release albumin fusion proteins and/or polynucleotides include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

[0439] Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

[0440] Sustained-release albumin fusion proteins and/or polynucleotides also include liposomally entrapped albumin fusion proteins and/or polynucleotides of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the*

Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the albumin fusion protein and/or polynucleotide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

[0441] In yet an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

[0442] Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

[0443] For parenteral administration, in one embodiment, the albumin fusion protein and/or polynucleotide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

[0444] Generally, the formulations are prepared by contacting the albumin fusion protein and/or polynucleotide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[0445] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at

the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[0446] The albumin fusion protein is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[0447] Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Albumin fusion proteins and/or polynucleotides generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0448] Albumin fusion proteins and/or polynucleotides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous albumin fusion protein and/or polynucleotide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized albumin fusion protein and/or polynucleotide using bacteriostatic Water-for-Injection.

[0449] In a specific and preferred embodiment, the Albumin fusion protein formulations comprises 0.01 M sodium phosphate, 0.15 mM sodium chloride, 0.16 micromole sodium octanoate/milligram of fusion protein, 15 micrograms/milliliter polysorbate 80, pH 7.2. In another specific and preferred embodiment, the Albumin fusion protein formulations consists 0.01 M sodium phosphate, 0.15 mM sodium chloride, 0.16 micromole sodium octanoate/milligram of fusion protein, 15 micrograms/milliliter

polysorbate 80, pH 7.2. The pH and buffer are chosen to match physiological conditions and the salt is added as a tonicifier. Sodium octanoate has been chosen due to its reported ability to increase the thermal stability of the protein in solution. Finally, polysorbate has been added as a generic surfactant, which lowers the surface tension of the solution and lowers non-specific adsorption of the albumin fusion protein to the container closure system.

[0450] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the albumin fusion proteins and/or polynucleotides of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the albumin fusion proteins and/or polynucleotides may be employed in conjunction with other therapeutic compounds.

[0451] The albumin fusion proteins and/or polynucleotides of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum*. In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with alum. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, *Haemophilus influenzae* B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever,

and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

Therapeutic Compositions Alone or in Combination

[0452] The albumin fusion proteins and/or polynucleotides of the invention may be administered alone or in combination with other therapeutic agents. Albumin fusion protein and/or polynucleotide agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include but are not limited to, GLP-1, insulin (including an insulin fragment or variant), an insulin secretagogue, IGF-1, an IGF-1 secretagogue, an insulin sensitizer (e.g., a Thiazolidinedione, or Resistin antagonist (e.g., anti-resistin antibody)), a beta cell growth factor, an alpha glucosidase inhibitor, a sulfonylureas, biguanide, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second. In preferred embodiments, this administration immediately prior to, during, or immediately after nutrient consumption (e.g., a meal).

[0453] In preferred embodiments, a composition of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered in combination with Glucagon-Like Peptide 1 or fragments or variants thereof (including fusion proteins containing GLP-1 peptides, fragments and/or variants). Glucagon-Like Peptide 1 that may

be administered in combination with a composition of the invention include, but are not limited to, AC-2993 (Exendin-4), insulinotropin (GLP-1-(7-37)), and NNC 90-1170.

[0454] In particular embodiments, the use of a composition of the invention in combination with Glucagon-Like Peptide 1 is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0455] In other preferred embodiments, a composition of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered in combination one or more with beta-cell growth factors. Beta-cell growth factors (Stewart et al., Journal of Clinical Endocrinology & Metabolism 86(3):984-988 (2001)) that may be administered in combination with a composition of the invention include, but are not limited to, betacellulin, exendin-4, glucagons-like peptide-1, hepatocyte growth factors, insulin-like growth factor-I, insulin-like growth factor-II, islet neogenesis-associated protein, placental lactogen, PTH-related protein, and cytokeratin 20 (Anastasi et al., Eur J Endocrinol 141(6):644-52 (1999)). In another preferred embodiment, a composition of the invention is administered in combination with RegIV (The RegIV gene and protein have also been identified by the names "Colon Specific Gene" and "Colon Specific Protein", respectively. See e.g., U.S. Patent No. 5,861,494, U.S. Patent No. 6,080,722, and PCT Publication No. WO96/39541).

[0456] In particular embodiments, the use of a composition of the invention in combination with one or more beta-cell growth factors is contemplated for the treatment (e.g., amelioration) or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0457] In other preferred embodiments, a composition of the invention is administered in combination with one or more alpha-glucosidase inhibitors. Alpha-Glucosidase inhibitors that may be administered in combination with a composition of the invention include, but are not limited to, miglitol (Glyset), acarbose (Precose), voglibose (Basen; Glustat).

[0458] In particular embodiments, the use of a composition of the invention in combination with one or more alpha-glucosidase inhibitors is contemplated for the treatment (e.g., amelioration) or prevention of diabetes mellitus, i.e., IDDM and/or

NIDDM and/or a condition associated with diabetes.

[0459] In other preferred embodiments, a composition of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered in combination with one or more insulin and related agents. Insulin and related agents that may be administered in combination with a composition of the invention include, but are not limited to, Insulin Mixtures (Humulin 50/50, Humulin 70/30, Novolin 70/30), intermediate acting insulin (Humulin L, Humulin N, Iletin II Lente, Iletin II NPH, Novolin L, Novolin N), long acting insulin (Humulin U, Lantus), rapid acting insulin (Humalog, Insulin lispro, Insulin Aspart), short acting insulin (Humulin R, Iletin II Regular, Novolin R, Novolin BR), AERx Insulin Inhaler, Basulin (Insulin Flamel), Inhaled Insulin, Insulin detemir (long-acting insulin, NN-304), Macrulin (oral insulin), Mecasermin (Somazon), Oral Insulin, Oralin (Oralgen, RapidMist), and Transfersulin (insulin, Transfersome).

[0460] In particular embodiments, the use of a composition of the invention in combination with one or more insulin and related agents is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes. In a highly preferred embodiment a composition of the invention is administered in combination with insulin and/or related molecules (e.g., insulin fragments and variants, and insulin secretagogues).

[0461] In other preferred embodiments, a composition of the invention ise administered in combination with one or more hormone inhibitors. Hormone inhibitors that may be administered in combination with a composition of the invention include, but are not limited to, BAY-27-9955 and pegvisomant (Somavert, Trovert).

[0462] In particular embodiments, the use of a composition of the invention in combination with one or more hormone inhibitors is contemplated for the treatment (e.g., amelioration) or prevention of conditions associated with diabetes mellitus, for example, diabetic retinopathy.

[0463] In particular embodiments, the use of a composition of the invention in combination with the mature (secreted) portion, the cysteine rich region(s), the precursor polypeptide, the propeptide polypeptide, or any fragment thereof, of one or more of the polypeptides selected from the group: TGF-β1, TGF-β2, TGF-β3, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12,

BMP-13, BMP-14, BMP-15, BMP-15, GDF-1, GDF-3, GDF-8, GDF-9, and MIS.

[0464] In other preferred embodiments, a composition of the invention is administered in combination with one or more sulfonylureas. Sulfonylureas that may be administered in combination with a composition of the invention include, but are not limited to, glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), chlorpropamide (Diabinese), acetohexamide (Dymelor), glipizide (Glucotrol, Glucotrol XL), tolbutamide (Orinase), tolazamide (Tolinase), gliclazide (Adianor), and glipentide (Staticum).

[0465] In particular embodiments, the use of a composition of the invention in combination with one or more sulfonylureas is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0466] In other preferred embodiments, a composition of the invention is administered in combination with one or more biguanides. Biguanides that may be administered in combination with a composition of the invention include, but are not limited to, metformin (Glucophage) and a combination of metformin with glibenclamide (Glucovance, Glucophage+Glyburide).

[0467] In particular embodiments, the use of a composition of the invention in combination with biguanides is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0468] In other preferred embodiments, a composition of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered in combination with one or more Thiazolidinediones (TZDs). Thiazolidinediones that may be administered in combination with a composition of the invention include, but are not limited to, rosiglitazone maleate (Avandia), pioglitazone hydrochloride (Actos), isaglitazone (MCC-555,RWJ241947), and troglitazone (Rezulin, Romozin, Prelay, Noscal.

[0469] In particular embodiments, the use of a composition of the invention in combination with one or more Thiazolidinediones is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0470] In other preferred embodiments, a composition of the invention is administered in combination with Resistin antagonists and/or anti-Resistin antibodies.

[0471] In other preferred embodiments, a composition of the invention is administered in combination with one or more other insulin sensitizers. Other Insulin Sensitizers that may be administered in combination with a Therapeutics of the invention include, but are not limited to, Bexarotene (Targretin), Chiro inositol (INS-1), Chromium picolinate (Chromax Plus; Chromax), Vanadium (KP-102, LP-100), and PPAR-gamma Activators which include, but are not limited to, GI-262570 (GW-2570), GW-409544 (GW-544), and KRP-297.

[0472] In other preferred embodiments, a composition of the invention is administered in combination with Resistin antagonists and/or anti-Resistin antibodies.

[0473] In particular embodiments, the use of a composition of the invention in combination with one or more insulin sensitizers is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0474] In other preferred embodiments, a composition of the invention is administered in combination with one or more non-sulfonylureas including Meglitinides. Non-Sulfonylureas that may be administered in combination with a composition of the invention include, but are not limited to, repaglinide (Prandin, Aculin), rateglinide (Starlix), BTS 67582, Mitiglinide (KAD-1229), and ProBeta.

[0475] In particular embodiments, the use of a composition of the invention in combination with one or more non-sulfonylureas is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0476] In preferred embodiments, a composition of the invention is administered in combination with one or more immunomodulators. Immunomodulators that may be administered in combination with a composition of the invention include, but are not limited to, AI-401, CDP-571 (anti-TNF monoclonal antibody), CG-1088, Diamyd (diabetes vaccine), ICM3 (anti-ICAM-3 monoclonal antibody), linomide (Roquinimex), NBI-6024 (altered peptide ligand), TM-27, VX-740 (HMR-3480), caspase 8 protease inhibitors, thalidomide, hOKT3gamma1 (Ala-ala) (anti-CD3 monoclonal antibody), Oral

Interferon-Alpha, oral lactobacillus, and LymphoStat-B™.

[0477] In particular embodiments, the use of a composition of the invention in combination with one or more immunomodulators is contemplated for the treatment (e.g,. amelioration) and/or prevention of autoimmune diabetes, i.e., IDDM Insulin-Dependent Diabetes Mellitus.

[0478] In still other preferred embodiments, a composition of the invention is administered in combination with one or more of the following: bromocriptine (Ergoset), etomoxir, iloprost (Endoprost), acetylcholine, ascorbic acid (Vitamin C), and antagonists of resistin (Steppan et al., Nature 409(6818):307-12 2001)) and is contemplated for the treatment (e.g., amelioration) and/or prevention of diabetes mellitus, i.e., IDDM and/or NIDDM and/or a condition associated with diabetes.

[0479] In one embodiment, a composition of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered in combination with an anticoagulant. Anticoagulants that may be administered with a compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADON™), acenocoumarol (e.g., nicoumalone, SINTHROME™), indan-1,3-dione, phenprocoumon (e.g., MARCUMAR™), ethyl biscoumacetate (e.g., TROMEXAN™), and aspirin. In a specific embodiment, a composition of the invention is administered in combination with heparin and/or warfarin. In another specific embodiment, a composition of the invention is administered in combination with warfarin. In another specific embodiment, a composition of the invention is administered in combination with warfarin and aspirin. In another specific embodiment, a composition of the invention is administered in combination with heparin. In another specific embodiment, a composition of the invention is administered in combination with heparin and aspirin.

[0480] In another embodiment, a composition of the invention is administered in combination with one or more thrombolytic drugs. Thrombolytic drugs that may be administered with a composition of the invention include, but are not limited to, plasminogen, lys-plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASE™), antiresplace (e.g., EMINASE™), tissue plasminogen activator (t-PA, altevase, ACTIVASE™), urokinase (e.g., ABBOKINASE™), sauruplase, (Prourokinase, single

chain urokinase), and aminocaproic acid (e.g., AMICAR™). In a specific embodiment, a composition of the invention is administered in combination with tissue plasminogen activator and aspirin.

[0481] In another embodiment, a composition of the invention is administered in combination with one or more antiplatelet drugs. Antiplatelet drugs that may be administered with a composition of the invention include, but are not limited to, aspirin, dipyridamole (e.g., PERSANTINE™), and ticlopidine (e.g., TICLID™).

[0482] In specific embodiments, the use of one or more anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with a composition of the invention is contemplated for the prevention, diagnosis, and/or treatment of thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of one or more anticoagulants, thrombolytic drugs and/or antiplatelet drugs in combination with a composition of the invention is contemplated for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for a composition of the invention, alone or in combination with one or more antiplatelet, anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0483] In certain embodiments, a composition of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered in combination with one or more antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with a composition of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the a composition of the invention, includes, but are not

limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with a composition of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, one or more antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with a composition of the invention to treat AIDS and/or to prevent or treat HIV infection.

[0484] Additional NRTIs that may be administered in combination with a composition of the invention, include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active, prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281).

[0485] Additional NRTIs that may be administered in combination with a composition of the invention, include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N

mutations); and Propolis (WO 99/49830).

[0486] Additional protease inhibitors that may be administered in combination with a composition of the invention, include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

[0487] Additional antiretroviral agents that may be administered in combination with a composition of the invention, include one or more fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

[0488] Additional antiretroviral agents that may be administered in combination with a composition of the invention, include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine receptor agonists such as RANTES, SDF-1, MIP-1α, MIP-1β, etc., may also inhibit fusion.

[0489] Additional antiretroviral agents that may be administered in combination with a composition of the invention, include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and

naphthols such as those disclosed in WO 98/50347.

[0490] Additional antiretroviral agents that may be administered in combination with a composition of the invention, include hydroxyurea-like compounds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors such as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

[0491] Additional antiretroviral agents that may be administered in combination with a composition of the invention, include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

[0492] Other antiretroviral therapies and adjunct therapies that may be administered in combination with a composition of the invention, include one or more cytokines and/or lymphokines such as, MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-α2a; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targeted to the ER to block surface expression of newly synthesized CCR5 (Yang et al., PNAS 94:11567-72 (1997); Chen et al., Nat. Med. 3:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF-α antibodies, and

monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α-naphthoflavone (WO 98/30213); and antioxidants such as γ-L-glutamyl-L-cysteine ethyl ester (γ-GCE; WO 99/56764).

[0493] In a further embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, remantidine, maxamine, or thymalfasin. Specifically, interferon albumin fusion protein can be administered in combination with any of these agents. Moreover, interferon alpha albumin fusion protein can also be admistered with any of these agents, and preferably, interferon alpha 2a or 2b albumin fusion protein can be administered with any of these agents. Furthermore, interferon beta albumin fusion protein can also be admistered with any of these agents. Additionally, any of the IFN hybrids albumin fusion proteins can be administered in combination with any of these agents.

[0494] In a most preferred embodiment, interferon albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon alpha albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon alpha 2a albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon alpha 2b albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, interferon beta albumin fusion protein is administered in combination with ribavirin. In a further preferred embodiment, hybrid interferon albumin fusion protein is administered in combination with ribavirin.

[0495] In other embodiments, a composition of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with a composition of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™,

FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, composition of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, a composition of the invention is used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, a composition of the invention is used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, a composition of the invention is used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, a Composition of the invention is used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, a Composition of the invention is used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, a Composition of the invention is used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, a Composition of the invention is used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

[0496] In a further embodiment, a composition of the invention is administered in combination with an antibiotic agent. Antibiotic agents that may be administered with a composition of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin,

chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

[0497] In other embodiments, a composition of the invention is administered in combination with one or more immunostimulants. Immunostimulants that may be administered in combination with a composition of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g., INOSIPLEX™), interferons (e.g., interferon alpha), and interleukins (e.g., IL-2).

[0498] In other embodiments, a Composition of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered in combination with one or more immunosuppressive agents. Immunosuppressive agents that may be administered in combination with a composition of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with a composition of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organs or bone marrow transplantation.

[0499] In an additional embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be

administered with the albumin fusion proteins and/or polynucleotides of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte glubulin), and GAMIMUNE™. In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0500] In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered alone or as part of a combination therapy, either in vivo to patients or in vitro to cells, for the treament of cancer. In a specific embodiment, the albumin fusion proteins, particularly IL-2-albumin fusions, are administered repeatedly during passive immunotherapy for cancer, such as adoptive cell transfer therapy for metastatic melanoma as described in Dudley *et al.* (Science Express, 19 September 2002., at www.scienceexpress.org, hereby incorporated by reference in its entirety).

[0501] In certain embodiments, a Compositions of the invention (i.e., albumin fusion proteins and/or polynucleotides of the invention) is administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with a composition of the invention include, but are not limited to, corticosteroids (e.g.,betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[0502] In an additional embodiment, a composition of the invention is administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may

be administered with a composition of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0503] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0504] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0505] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0506] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen

crab shells), (Murata et al., Cancer Res. 51:22-2 6(1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326 (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480 (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446 (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664 (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

[0507] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (Brem et al., J Pediatr. Surg. 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (Storgard et al., J Clin. Invest. 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[0508] Anti-angiogenic agents that may be administed in combination with a compound of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of

angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with a compositon of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with a compositon of the invention include, but are not limited to, EMD-121974 (Merck KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with a compositon of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with a compositon of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[0509] In particular embodiments, the use of a composition of the invention in combination with one or more anti-angiogenic agents is contemplated for the treatment (e.g., amelioration) and/or prevention of an autoimmune disease, such as for example, an autoimmune disease described herein.

[0510] In a particular embodiment, the use of a composition of the invention in combination with one or more anti-angiogenic agents is contemplated for the treatment (amelioration) and/or prevention of arthritis. In a more particular embodiment, the use of a composition of the invention in combination with anti-angiogenic agents is contemplated for the treatment (amelioration) and/or prevention of rheumatoid arthritis.

[0511] In another embodiment, the polynucleotides encoding a polypeptide of the

present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[0512] In additional embodiments, a composition of the invention is administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with a composition of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example,

Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

[0513] In one embodiment, a composition of the invention is administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

[0514] In a specific embodiment, a composition of the invention is administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, a compositions of the invention is administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, a composition of the invention is administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, a composition of the invention is administered in combination with Rituximab. In a further embodiment, a composition of the invention is administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, a composition of the invention is administered in combination with tositumomab. In a further embodiment, a composition of the invention is administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

[0515] In another specific embodiment, a composition of the invention is administered in combination Zevalin™. In a further embodiment, a composition of the invention is

administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are ^{90}Y and ^{111}In.

[0516] In an additional embodiment, a composition of the invention is administered in combination with one or more cytokines. Cytokines that may be administered with a composition of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, a Composition of the invention may be administered with an interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

[0517] In one embodiment, a composition of the invention is administered in combination with one or more members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with a composition of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[0518] In an additional embodiment, a composition of the invention is administered in combination with one or more angiogenic proteins. Angiogenic proteins that may be administered with a composition of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816;

Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

[0519] In an additional embodiment, a composition of the invention is administered in combination with one or more Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with a composition of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[0520] In an additional embodiment, a composition of the invention is administered in combination with one or more hematopoietic growth factors. Hematopoietic growth factors that may be administered with a composition of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

[0521] In certain embodiments, a composition of the invention is administered in combination with one or more adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

[0522] In another embodiment, a composition of the invention is administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

[0523] In another embodiment, a composition of the invention is administered in combination with one or more diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit Na^+-K^+-$2Cl^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

[0524] In one embodiment, a composition of the invention is administered in combination with one or more treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I, radioactive isotopes of iodine such as ^{131}I and ^{123}I; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin

agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T_4™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T_3™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca^{2+} channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

[0525] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl

estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

[0526] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone

acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone); bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), ciglitazone, pioglitazone, and alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide).

[0527] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide),

DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), PRECOSE™ (acarbose), AMARYL™ (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIA™ (rosiglitazone maleate) ACTOS™ (piogliatazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide).

[0528] In still other embodiments, a composition of the invention is administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

[0529] In one embodiment, a composition of the invention is administered in combination with one or more treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estsradiol (e.g., FEMHRT™).

[0530] In an additional embodiment, a composition of the invention is administered in combination with one or more drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B_{12}, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin, folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

[0531] In certain embodiments, a composition of the invention is administered in combination with one or more agents used to treat psychiatric disorders. Psychiatric drugs

that may be administered with a composition of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

[0532] In other embodiments, a composition of the invention is administered in combination with one or more agents used to treat neurological disorders. Neurological agents that may be administered with a composition of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benztropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g., riluzole).

[0533] In another embodiment, a composition of the invention is administered in combination with one or more vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with a composition of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with a composition of the invention include, but are not limited to amlodipine, bepridil,

diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

[0534] In certain embodiments, a composition of the invention is administered in combination with one or more treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with a composition of the invention include, but are not limited to, H_2 histamine receptor antagonists (e.g., TAGAMET™ (cimetidine), ZANTAC™ (ranitidine), PEPCID™ (famotidine), and AXID™ (nizatidine)); inhibitors of H^+, K^+ ATPase (e.g., PREVACID™ (lansoprazole) and PRILOSEC™ (omeprazole)); Bismuth compounds (e.g., PEPTO-BISMOL™ (bismuth subsalicylate) and DE-NOL™ (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g., CYTOTEC™ (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTIL™ (diphenoxylate), MOTOFEN™ (diphenoxin), and IMODIUM™ (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN™ (octreotide), antiemetic agents (e.g., ZOFRAN™ (ondansetron), KYTRIL™ (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, trifluprομazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

[0535] In additional embodiments, a composition of the invention is administered in combination with one or more other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

[0536] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions comprising albumin fusion proteins of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Gene Therapy

[0537] Constructs encoding albumin fusion proteins of the invention can be used as a part of a gene therapy protocol to deliver therapeutically effective doses of the albumin fusion protein. A preferred approach for *in vivo* introduction of nucleic acid into a cell is by use of a viral vector containing nucleic acid, encoding an albumin fusion protein of the invention. Infection of cells with a viral vector has the advantage that a large proportion of the targeted cells can receive the nucleic acid. Additionally, molecules encoded within the viral vector, *e.g.*, by a cDNA contained in the viral vector, are expressed efficiently in cells which have taken up viral vector nucleic acid.

[0538] Retrovirus vectors and adeno-associated virus vectors can be used as a recombinant gene delivery system for the transfer of exogenous nucleic acid molecules encoding albumin fusion proteins *in vivo*. These vectors provide efficient delivery of nucleic acids into cells, and the transferred nucleic acids are stably integrated into the chromosomal DNA of the host. The development of specialized cell lines (termed "packaging cells") which produce only replication-defective retroviruses has increased the utility of retroviruses for gene therapy, and defective retroviruses are characterized for use in gene transfer for gene therapy purposes (for a review see Miller, A.D. (1990) *Blood* 76:27 1). A replication defective retrovirus can be packaged into virions which can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F.M. *et al.*, (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals.

[0539] Another viral gene delivery system useful in the present invention uses adenovirus-derived vectors. The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner *et al., BioTechniques* 6:616 (1988); Rosenfeld *et al.*, Science 252:431-434 (1991); and Rosenfeld *et al., Cell* 68:143-155 (1992). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (*e.g.*, Ad2, Ad3, Ad7 etc.) are known to those

skilled in the art. Recombinant adenoviruses can be advantageous in certain circumstances in that they are not capable of infecting nondividing cells and can be used to infect a wide variety of cell types, including epithelial cells (Rosenfeld *et al.*, (1992) cited supra). Furthermore, the virus particle is relatively stable and amenable to purification and concentration, and as above, can be modified so as to affect the spectrum of infectivity. Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situations where introduced DNA becomes integrated into the host genome (*e.g.*, retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner *et al.*, cited supra; Haj-Ahmand *et al.*, J. Virol. 57:267 (1986)).

[0540] In another embodiment, non-viral gene delivery systems of the present invention rely on endocytic pathways for the uptake of the subject nucleotide molecule by the targeted cell. Exemplary gene delivery systems of this type include liposomal derived systems, poly-lysine conjugates, and artificial viral envelopes. In a representative embodiment, a nucleic acid molecule encoding an albumin fusion protein of the invention can be entrapped in liposomes bearing positive charges on their surface (*e.g.*, lipofectins) and (optionally) which are tagged with antibodies against cell surface antigens of the target tissue (Mizuno *et al.* (1992) *No Shinkei Geka* 20:547-5 5 1; PCT publication W091/06309; Japanese patent application 1047381; and European patent publication EP-A-43075).

[0541] Gene delivery systems for a gene encoding an albumin fusion protein of the invention can be introduced into a patient by any of a number of methods. For instance, a pharmaceutical preparation of the gene delivery system can be introduced systemically, *e.g.* by intravenous injection, and specific transduction of the protein in the target cells occurs predominantly from specificity of transfection provided by the gene delivery vehicle, cell-type or tissue-type expression due to the transcriptional regulatory sequences controlling expression of the receptor gene, or a combination thereof. In other embodiments, initial delivery of the recombinant gene is more limited with introduction into the animal being quite localized. For example, the gene delivery vehicle can be introduced by catheter (see U.S. Patent 5,328,470) or by Stereotactic injection (*e.g.* Chen

et al. (1994) *PNAS* 91: 3 054-3 05 7). The pharmaceutical preparation of the gene therapy construct can consist essentially of the gene delivery system in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Where the albumin fusion protein can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can comprise one or more cells which produce the albumin fusion protein.

Additional Gene Therapy Methods

[0542] Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of an albumin fusion protein of the invention. This method requires a polynucleotide which codes for an albumin fusion protein of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the fusion protein by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[0543] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide encoding an albumin fusion protein of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the fusion protein of the present invention. Such methods are well-known in the art. For example, see Belldegrun et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini et al., Cancer Research 53: 1107-1112 (1993); Ferrantini et al., J. Immunology 153: 4604-4615 (1994); Kaido et al., Int. J. Cancer 60: 221-229 (1995); Ogura et al., Cancer Research 50: 5102-5106 (1990); Santodonato et al., Human Gene Therapy 7:1-10 (1996); Santodonato et al., Gene Therapy 4:1246-1255 (1997); and Zhang et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0544] As discussed in more detail below, the polynucleotide constructs can be

delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0545] In one embodiment, polynucleotides encoding the albumin fusion proteins of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, polynucleotides encoding the albumin fusion proteins of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[0546] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0547] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the gene corresponding to the Therapeutic protein portion of the albumin fusion proteins of the invention.

[0548] Unlike other gene therapy techniques, one major advantage of introducing

naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0549] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0550] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0551] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial

tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0552] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0553] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0554] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7416 (1987), which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA 86:6077-6081 (1989), which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. 265:10189-10192 (1990), which is herein incorporated by reference), in functional form.

[0555] Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA 84:7413-7416 (1987), which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[0556] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., Felgner et al., Proc. Natl. Acad. Sci. USA

84:7413-7416 (1987), which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0557] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0558] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0559] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid

film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+}-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta 394:483 (1975); Wilson et al., Cell 17:77 (1979)); ether injection (Deameret al., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch et al., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka et al., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

[0560] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0561] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[0562] In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding an albumin fusion protein of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0563] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0564] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding an albumin fusion protein of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a fusion protein of the present invention.

[0565] In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses fusion protein of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al. Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1992)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al., Proc. Natl. Acad. Sci. USA 76:6606 (1979)).

[0566] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993);

Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0567] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0568] In certain other embodiments, the cells are engineered, ex vivo or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0569] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses,

vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a fusion protein of the invention.

[0570] Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein incorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[0571] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0572] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[0573] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered

by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0574] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0575] The polynucleotide encoding an albumin fusion protein of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0576] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0577] A preferred method of local administration is by direct injection. Preferably, an albumin fusion protein of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0578] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo

surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0579] Therapeutic compositions useful in systemic administration, include fusion proteins of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising albumin fusion proteins of the invention for targeting the vehicle to a particular site.

[0580] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281 (1992), which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[0581] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0582] Albumin fusion proteins of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

[0583] Assays described herein or otherwise known in the art may be applied or routinely modified to test for one or more biological activities (e.g., as described in Table 1, column 2, and in Examples 28-35, for example, Example 28: [^{3}H]-2-Deoxyglucose Uptake Assay, Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines, Example 30: Assaying for Glycosuria, Example 31: Occurrence of Diabetes in NOD Mice, Example 32: Histological Examination of NOD Mice, Example 33: Pancreatic Beta-Cell Transplantation Combination Therapy, Example 34: *In vivo* Mouse Model of NIDDM, Example 35: *In vitro* H4IIe –SEAP Reporter Assays Establishing Involvement in Insulin Action) of the albumin fusion proteins of the invention (including fragments and/or variants of the albumin fusion proteins of the invention) and/or of the biologically active and/or therapeutically active fragments and/or variants of the Therapeutic protein portion of albumin fusion proteins of the invention. If an albumin fusion protein and/or therapeutic protein portion of an albumin fusion protein exhibits an activity in a particular assay, it is likely that the Therapeutic protein corresponding to the fusion protein may be involved in the diseases associated with the biological activity. Thus, the fusion protein could be used to treat the associated disease or disorder.

[0584] The present invention encompasses methods of treating (e.g., ameliorating) or preventing a disease, disorder and/or a condition associated with the disease or disorder, comprising administering to a patient in which such treatment or prevention is desired an albumin fusion protein of the invention. In preferred embodiments, the present invention encompasses a method of treating or preventing a disease or disorder listed in the "Preferred Indication Y" column of Table 1, comprising administering to a patient in which such treatment or prevention is desired an albumin fusion protein of the invention that comprises a Therapeutic protein portion corresponding to a Therapeutic protein (or fragment or variant thereof) disclosed in the "Therapeutic Protein: X" column of Table 1 (in the same row as the disease or disorder to be treated is listed in the "Preferred Indication Y" column of Table 1) in an amount effective to treat or prevent the disease or disorder.

[0585] In certain embodiments, an albumin fusion protein of the present invention may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the gene corresponding to the Therapeutic protein portion of the fusion protein of the invention is expressed.

[0586] In another preferred embodiment, the "Therapeutic protein" portion of an albumin fusion protein of the invention and/or an albumin fusion protein of the invention can be used to treat (e.g., ameliorate) or prevent a metabolic/endocrine disease or disorder. In a highly preferred embodiment, the metabolic/endocrine disease or disorder is diabetes and/or a condition associated with diabetes. As a non-limiting example, a "Therapeutic protein" may be one that regulates glucose uptake by cells, that binds specifically to a particular cell type (e.g., normal adipocytes, myotubes, hepatocytes, and pancreatic beta cells of the Islet of Langerhans, and/or abnormal (e.g., cancer cell or insulin-resistant adipocytes, myotubes, and hepatocytes)), that enhances insulin sensitivity in insulin-responsive tissues, and/or that regulates hepatic glucose output, and therefore may be used to target a compound (drug, or cytotoxic agent) to that cell type specifically.

[0587] Thus, the present invention encompasses a method of treating (e.g., ameliorating) or preventing a metabolic/endocrine disorder comprising administering to a patient in which such treatment or prevention is desired an albumin fusion protein of the invention.

[0588] Malfunctioning of any step(s) in insulin secretion and/or action can lead to many metabolic/endocrine disorders (e.g., the dysregulation of oxygen utilization, adipogenesis, glycogenesis, lipogenesis, glucose uptake, protein synthesis, thermogenesis, and maintenance of the basal metabolic rate) and is associated with diseases and/or disorders that include, but are not limited to, hyperinsulinemia, insulin resistance, insulin deficiency, hyperglycemia, hyperlipidemia, hyperketonemia, and diabetes. In preferred embodiments, an albumin fusion protein of the invention is administered to a patient (preferably a human) to treat or prevent an insulin related disease or disorder, and/or a condition associated with an insulin related disease or disorder. In specific embodiments and albumin fusion protein of the invention is administered to treat or prevent a disease, disorder, or condition, characterized by a state of insulin resistance. Disorders characterized by insulin resistance that can be treated (e.g., ameliorated), prevented,

diagnosed, and/or prognosed using a fusion protein of the invention include, but are not limited to, NIDDM, obesity, hypertension, hyperglycemia, heart disease, renal failure, androgen excess, and liver cirrhosis or liver disease, injury and/or a complication associated with transplantation.

[0589] In further, specific embodiments, a fusion protein of the invention is administered to treat or prevent hyperinsulinemia or a disorder or a condition associated with hyperinsulinemia.

[0590] In another embodiment, the invention provides a method of increasing the sensitivity of a cell to insulin comprising contacting a cell with an albumin fusion protein of the invention. In one embodiment, this method is performed *in vitro*. In another embodiment this method is performed *in vitro*. In specific embodiments, the cell contacted according to this method is a liver cell, an adipocyte, a kidney cell, a skin cell, a bone cell, or a skeletal muscle cell.

[0591] In a preferred embodiment, the "Therapeutic protein" portion of an albumin fusion protein of the invention and/or an albumin fusion protein of the invention can be used to treat (e.g., ameliorate) or prevent diabetes mellitus and/or a condition associated with diabetes mellitus. Thus, in a preferred embodiment, the present invention encompasses a method of treating (e.g., ameliorating) or preventing diabetes mellitus and/or one or more conditions associated with diabetes mellitus, comprising administering to a patient in which such treatment or prevention is desired an albumin fusion protein of the invention.

[0592] In another preferred embodiment, the present invention encompasses a method of treating (e.g., ameliorating) or preventing a condition associated with diabetes mellitus, comprising administering to a patient in which such a treatment or prevention is desired an albumin fusion protein of the invention. Conditions that may be treated or prevented using an albumin fusion protein of the invention include, but are not limited to, obesity, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and/or other diseases and disorders as described in the "Cardiovascular Disorders" section below), blood vessel blockage, gangrene, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and

disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), vision impairment (e.g., diabetic retinopathy, cataract, and blindness), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, dyslipidemia (e.g., hyperlipidemia), hyperglycemia, hyperketonemia, ketoacidosis, endocrine disorders (e.g., hyperinsulinemia, insulin insensitivity, insulin resistance, and/or an endocrine disorder as described in the "Endocrine Disorders" section below), ulcers, impaired wound healing, infection (e.g., an infectious disease or disorder as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture, and and/or an immune system disease or disorder (e.g., anemia, impaired white blood cell function, and/or an immune system disease or disorder as described in the "Immune Activity" section below).

[0593] In a most preferred embodiment, the "Therapeutic protein" portion of an albumin fusion protein of the invention and/or an albumin fusion protein of the invention can be used to treat (e.g., ameliorate) or prevent type II diabetes and/or a condition associated with type II diabetes. Thus, in a preferred embodiment, the present invention encompasses a method of treating (e.g., ameliorating) or preventing type II diabetes mellitus and/or one or more conditions associated with type II diabetes mellitus, comprising administering to a patient in which such treatment or prevention is desired an albumin fusion protein of the invention.

[0594] In another preferred embodiment, the present invention encompasses a method of treating (e.g., ameliorating) or preventing a condition associated with type II diabetes mellitus, comprising administering to a patient in which such a treatment or prevention is desired an albumin fusion protein of the invention. Conditions that may be treated or prevented using an albumin fusion protein of the invention include, but are not limited to, obesity, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and/or other diseases and disorders as described in the "Cardiovascular Disorders" section below), blood vessel blockage, gangrene, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve

disease and nerve damage (e.g., due to diabetic neuropathy), vision impairment (e.g., diabetic retinopathy, cataract, and blindness), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, dyslipidemia (e.g., hyperlipidemia), hyperglycemia, hyperketonemia, ketoacidosis, endocrine disorders (e.g., hyperinsulinemia, insulin insensitivity, insulin resistance, and/or an endocrine disorder as described in the "Endocrine Disorders" section below), ulcers, impaired wound healing, infection (e.g., an infectious disease or disorder as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture, and and/or an immune system disease or disorder (e.g., anemia, impaired white blood cell function, and/or an immune system disease or disorder as described in the "Immune Activity" section below).

[0595] In another preferred embodiment, the "Therapeutic protein" portion of an albumin fusion protein of the invention and/or an albumin fusion protein of the invention can be used to treat (e.g., ameliorate) or prevent type I diabetes and/or a condition associated with type I diabetes. Accordingly, in another preferred embodiment, the present invention encompasses a method of treating (e.g., ameliorating) or preventing type I diabetes mellitus and/or one or more conditions associated with type I diabetes mellitus, comprising administering to a patient in which such treatment or prevention is desired an albumin fusion protein of the invention.

[0596] In another preferred embodiment, the present invention encompasses a method of treating (e.g., ameliorating) or preventing a condition associated with type I diabetes mellitus, comprising administering to a patient in which such a treatment or prevention is desired an albumin fusion protein of the invention. Conditions that may be treated or prevented using an albumin fusion protein of the invention include, but are not limited to, obesity, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and/or other diseases and disorders as described in the "Cardiovascular Disorders" section below), blood vessel blockage, gangrene, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), vision impairment (e.g.,

diabetic retinopathy, cataract, and blindness), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, dyslipidemia (e.g., hyperlipidemia), hyperglycemia, hyperketonemia, ketoacidosis, endocrine disorders (e.g., hyperinsulinemia, insulin insensitivity, insulin resistance, and/or an endocrine disorder as described in the "Endocrine Disorders" section below), ulcers, impaired wound healing, infection (e.g., an infectious disease or disorder as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture, and and/or an immune system disease or disorder (e.g., anemia, impaired white blood cell function, and/or an immune system disease or disorder as described in the "Immune Activity" section below).

[0597] In an additional embodiment, a fusion protein of the invention is administered to a patient (preferably a human) to modulate (e.g., increase) the effect of insulin on blood glucose levels.

[0598] In a most preferred embodiment, an albumin fusion protein of the invention is administered to a patient to modulate or maintain glucose homeostasis.

[0599] In a preferred embodiment, the present invention provides a method of increasing glucose uptake in a cell using a fusion protein of the invention, comprising contacting a fusion protein of the invention with the cell in which an increase in glucose uptake is desired. In specific embodiments, the invention provides a method of increasing glucose uptake into a cell using a fusion protein of the invention *in vitro*. In other specific embodiments, the invention provides a method of increasing glucose uptake into a cell using a fusion protein of the invention *in vivo*. In preferred embodiments, the invention provides a method of increasing glucose uptake into a adipose cells. In other preferred embodiments, the invention provides a method of increasing glucose uptake into a skeletal cell. In other preferred embodiments, the invention provides a method of increasing glucose uptake into a liver cells

[0600] In a preferred embodiment, a fusion protein of the invention is used to treat or prevent a disease and disorder associated with aberrant glucose metabolism or glucose uptake into cells.

[0601] In another preferred embodiment, a fusion protein of the invention is administered to a patient (preferably a human) to regulate glucose metabolism. In a highly

preferred embodiment, a fusion protein of the invention, is administered to a patient (preferably a human) to increase glucose metabolism.

[0602] In one embodiment, an albumin fusion protein of the invention is administered to a patient (preferably a human) to lower glucose production in liver and/or other cells.

[0603] In another embodiment, a fusion protein of the invention is administered to a patient (preferably a human) to reduce gluconeogenesis in liver and/or other cells.

[0604] In one embodiment, the invention provides a method of decreasing glucose production of a cell comprising contacting a cell with a fusion protein of the invention. In one embodiment, this method is performed *in vitro*. In another embodiment this method is performed *in vitro*. In specific embodiments, the cell contacted according to this method is a liver cell, an adipocyte, a kidney cell, or a muscle cell.

[0605] In another preferred embodiment, a fusion protein of the invention is administered to a patient (preferably a human) to treat or prevent a disease or disorder selected from the group: glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, and cholesterol metabolism, and hepatocarcinomas.

[0606] In a further preferred embodiment, a fusion protein of the invention is administered to a patient to treat or prevent hyperglycemia and/or a condition associated with hyperglycemia. Conditions associated with hyperglycemia that can be treated or prevented using fusion proteins of the invention include, for example, type II and/or type I diabetes mellitus, obesity, kidney disease or impaired kidney function, nerve disease and/or damage (e.g., mononeuropathy, polyneuropathy, and malfunctioning of the autonomic nervous system) retinopathy, cataract, heart disease, hypertension, atherosclerosis, stroke, gangrene (e.g., of the feet and hands), impotence, infections, cataract, impaired white blood cell function, Carpal tunnel syndrome, Dupuytren's contracture, and diabetic ketoacidosis. In a further preferred embodiment, a fusion protein of the invention is administered in combination (e.g., concomitantly or serially) with a bolus administration of another diabetes Therapeutic (e.g., a bolus insulin treatment at time of food consumption) to modulate post-prandial hyperglycemia.

[0607] In other embodiments, embodiments, a fusion protein of the invention is administered to a patient to treat or prevent dyslipidemia or a condition associated with

dyslipidemia.

[0608] In other embodiments, embodiments, a fusion protein of the invention is administered to a patient to treat or prevent hyperlipidemia or a condition associated with hyperlipidemia.

[0609] In other embodiments, embodiments, a fusion protein of the invention is administered to a patient to treat or prevent hyperketonemia or a condition associated with hyperketonemia.

[0610] In a highly preferred embodiment, a fusion protein of the invention is administered to a patient to treat or prevent obesity or a condition associated with obesity.

[0611] In a preferred embodiment, a fusion protein of the invention is administered to a patient to limit weight gain.

[0612] In another preferred embodiment, a fusion protein of the invention is administered to a patient for the patient to lose weight.

[0613] In other preferred embodiments, embodiments, a fusion protein of the invention is administered to a patient to suppress appetite.

[0614] In other preferred embodiments, a fusion protein of the invention is administered to a patient to increase appetite.

[0615] In a further embodiment, the present invention provides a method of activating the leptin receptor using a fusion protein of the invention. In specific embodiments, the invention provides a method of activating the leptin receptor using a fusion protein of the invention *in vitro*. In other specific embodiments, the invention provides a method of activating the leptin receptor using a fusion protein of the invention *in vivo*.

[0616] In other preferred embodiments, a fusion protein of the invention is administered to a patient to alter or regulate nutritional partitioning in the patient. In one embodiment, an albumin fusion protein of the invention is administered according to this method to reduce fat mass. In another embodiment, an albumin fusion protein of the invention is administered according to this method to increase muscle mass.

[0617] In other preferred embodiments, a fusion protein of the invention is administered to a patient to promote weight gain.

[0618] In another preferred embodiment, a fusion protein of the invention is used to treat or prevent cardiovascular disease. In one embodiment, a fusion protein of the

invention is used to treat or prevent heart disease. In another embodiment, a fusion protein of the invention is used to treat or prevent atherosclerosis. In another embodiment, a fusion protein of the invention is used to treat or prevent hypertension or a condition associated with hypertension. In another embodiment, a fusion protein of the invention is used to treat or prevent coronary artery disease or a condition associated with coronary artery disease.

[0619] In another embodiment, a fusion protein of the invention can be used to treat or prevent neurological diseases, including but not limited to, Parkinson's disease, Alzheimer's disease, and/or as described herein under the section heading "Neural Activity and Neurological Diseases".

[0620] In another embodiment, a fusion protein of the invention is used to treat or prevent a neuropathy, neural injury, or a condition associated with a neuropathy or neural injury. Neuropathies that can be treated or prevented using a composition of the invention include, but are not limited to, retinopathy, autonomic neuropathy, parasympathetic neuropathy, and polyneuropathy. In a preferred embodiment, a composition of the invention is used to treat or prevent a paraympathetic neuropathy or parasympathetic neural injury and/or a condition associated with paraympathetic neuropathy or parasympathetic neural injury. In a highly preferred embodiment, a composition of the invention is used to treat or prevent a hepatic paraympathetic neuropathy or hepatic parasympathetic neural injury, and/or a condition associated with a hepatic paraympathetic neuropathy or hepatic parasympathetic neural injury.

[0621] In another preferred embodiment, the present invention provides a method of differentiating pancreatic ductal epithelial cells into insulin secreting pancreatic beta cells. In specific embodiments, the invention provides a method of differentiating pancreatic ductal epithelial cells into insulin secreting pancreatic beta cells using a fusion protein of the invention *in vitro*. In other specific embodiments, the invention provides a method of differentiating pancreatic ductal epithelial cells into insulin secreting pancreatic beta cells using a fusion protein of the invention *in vivo*. In still another preferred embodiment, the present invention provides a method of inducing proliferation of insulin secreting pancreatic beta cells using a fusion protein of the invention. In specific embodiments, the invention provides a method of inducing proliferation of insulin secreting pancreatic beta

cells using a fusion protein of the invention *in vitro*. In other specific embodiments, the invention provides a method of inducing proliferation of insulin secreting pancreatic beta cells using a fusion protein of the invention *in vivo*.

[0622] In a further preferred embodiment, the present invention provides a method of activating GSK3 kinase activity using a fusion protein of the invention. In specific embodiments, the invention provides a method of activating GSK3 kinase activity using a fusion protein of the invention *in vitro*. In other specific embodiments, the invention provides a method of activating GSK3 kinase activity using a fusion protein of the invention *in vivo*.

[0623] The, fusion proteins of the invention are useful in the treatment (e.g., amelioration), prevention, diagnosis, and/or detection of diseases and/or disorders associated with activities that include, but are not limited to, prohormone activation in the pancreatic, muscle, and fat tissues, cellular signaling in the pancreatic, muscle, and fat tissues, cellular proliferation in the pancreas, cellular differentiation of the pancreatic ductal epithelial cells and the fibroblasts in the stromal-vasculature in fat tissue, cell migration, and neurotransmitter activity.

[0624] In preferred embodiments, fusion proteins of the present invention may be used in the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders relating to diseases and disorders of the endocrine system (see, for example, "Endocrine Disorders" section below), the nervous system (see, for example, "Neurological Disorders" section below), the immune system (see, for example, "Immune Activity" section below), respiratory system (see, for example, "Respiratory Disorders" section below), cardiovascular system (see, for example, "Cardiovascular Disorders" section below), reproductive system (see, for example, "Reproductive System Disorders" section below) digestive system (see, for example, "Gastrointestinal Disorders" section below), diseases and/or disorders relating to cell proliferation (see, for example, "Hyperproliferative Disorders" section below), and/or diseases or disorders relating to the blood (see, for example, "Blood-Related Disorders" section below).

[0625] In another embodiment, a fusion protein of the invention is used to treat or prevent inflammatory and/or autoimmune disorders, including but not limited to, lupus, scleroderma, dermatomyositis, and/or as described herein under the section heading

"Immune Activity".

[0626] In another embodiment, a fusion protein of the invention is used to treat or prevent of a disease, disorder, and/or condition involving aberrant cellular proliferation, including but not limited to a preneoplastic disorder (e.g., hyperplasia, metaplasia, and dysplasia), a neoplastic disorder (e.g., cancer of the liver, lung, and colon), and/or as described herein under the section headings "Hyperproliferative Disorders" and "Diseases at the Cellular Level".

[0627] In a further embodiment, a fusion protein of the invention is used to promote wound healing or tissue regeneration, such as described below under the section headings "Wound Healing and Epithelial Cell Proliferation" and "Regeneration".

[0628] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is an insulin albumin fusion protein.

[0629] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a GLP1 albumin fusion protein.

[0630] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is an Exendin-4 albumin fusion protein.

[0631] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a HLDOU18 albumin fusion protein.

[0632] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a resistin albumin fusion proteins.

[0633] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a leptin albumin fusion proteins.

[0634] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a HCEIP80 albumin fusion protein.

[0635] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is an IGF1 albumin fusion protein.

[0636] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is an IFNa albumin fusion protein.

[0637] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a RegIV albumin fusion protein.

[0638] In a further preferred embodiment, the albumin fusion protein administered

according to the methods of the present invention is a HDRMI82 albumin fusion protein.

[0639] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a IL-22 albumin fusion protein.

[0640] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a IL-22 albumin fusion protein.

[0641] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is Interferon beta albumin fusion protein.

[0642] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a TR6 albumin fusion protein.

[0643] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is TNFR2 albumin fusion protein.

[0644] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is ACE2 inhibitor albumin fusion protein.

[0645] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is an interferon hybrid albumin fusion protein.

[0646] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a HWHGZ51 albumin fusion protein.

[0647] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a C17 albumin fusion protein.

[0648] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a somatostatin albumin fusion protein.

[0649] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a HDALV07 albumin fusion protein.

[0650] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a C peptide albumin fusion protein.

[0651] In a further preferred embodiment, the albumin fusion protein administered according to the methods of the present invention is a Wnt10b albumin fusion protein.

[0652] In a further preferred embodiment, the albumin fusion protein administered

according to the methods of the present invention is a CART albumin fusion protein.

[0653] The fusion proteins of the present invention can be used in the diagnosis, prognosis, prevention and/or treatment of one or more diseases, disorders and/or conditions of the endocrine system (see, for example, "Endocrine Disorders" section below). In other embodiments, a fusion protein of the present invention can be used in the diagnosis, prognosis, prevention, and/or treatment of one or more diseases, disorders and/or conditions of the digestive system (see, for example, "Gastrointestinal Disorders" section below). In other embodiments, a fusion protein of the present invention can be used in the diagnosis, prognosis, prevention, and/or treatment of one or more diseases, disorders and/or conditions of the nervous system (see, for example, "Neurological Disorders" section below), the immune system (see, for example, "Immune Activity" section below), respiratory system (see, for example, "Respiratory Disorders" section below), cardiovascular system (see, for example, "Cardiovascular Disorders" section below), reproductive system (see, for example, "Reproductive System Disorders" section below), diseases, disorders, and/or conditions relating to cell proliferation (see, for example, "Hyperproliferative Disorders" section below), and/or diseases, disorders and/or conditions of the blood (see, for example, "Blood-Related Disorders" section below).

[0654] In certain embodiments, an albumin fusion protein of the present invention may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the gene corresponding to the Therapeutic protein portion of the fusion protein of the invention is expressed.

[0655] Thus, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention are useful in the diagnosis, detection and/or treatment of diseases and/or disorders associated with activities that include, but are not limited to, prohormone activation, neurotransmitter activity, cellular signaling, cellular proliferation, cellular differentiation, and cell migration.

[0656] More generally, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may be useful for the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders associated with the following systems.

Endocrine Disorders

[0657] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

[0658] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[0659] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[0660] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma–islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling

defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[0661] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[0662] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

[0663] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin protein of the invention is expressed.

Gastrointestinal Disorders

[0664] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

[0665] Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric

retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess;).

[0666] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata, Echinococcus granulosus, Diphyllobothrium spp.*, and *T. solium*).

[0667] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases,

epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

[0668] Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

[0669] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

[0670] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases

[proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

[0671] Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms,

pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Regeneration

[0672] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

[0673] Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

[0674] Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could also be used prophylactically in an effort to

avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

[0675] Similarly, nerve and brain tissue could also be regenerated by using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

Wound Healing and Epithelial Cell Proliferation

[0676] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins

of the invention, could be used to promote dermal reestablishment subsequent to dermal loss

[0677] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to promote skin strength and to improve the appearance of aged skin.

[0678] It is believed that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[0679] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may have a cytoprotective effect on the small intestine mucosa. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion

proteins of the invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[0680] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to treat diseases associate with the under expression.

[0681] Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to prevent and heal damage to the lungs due to various pathological states. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema,

which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

[0682] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[0683] In addition, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Diseases at the Cellular Level

[0684] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer,

testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0685] In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

[0686] Additional diseases or conditions associated with increased cell survival that could be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma,

astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0687] Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognesed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Renal Disorders

[0688] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

[0689] Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative

glomerulonephritis I ′ and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

[0690] In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

[0691] Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

[0692] Compositions of the invention may be administered using any method known in

the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Compositions of the invention may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides of the invention are described in more detail herein.

Neural Activity and Neurological Diseases

[0693] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative

process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[0694] In one embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

[0695] In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins

of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

[0696] In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

[0697] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, *10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, *70*:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, *4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[0698] In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection,

exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

[0699] Further, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

[0700] Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral

ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

[0701] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat and/or detect neurologic diseases. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

[0702] Examples of neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

[0703] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis

such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

[0704] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

[0705] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

[0706] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

[0707] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup

Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

[0708] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision

defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

[0709] Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann

Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Immune Activity

[0710] Albumin fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as a marker or detector of a particular immune system disease or disorder.

[0711] In another embodiment, a fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed.

[0712] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-

onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[0713] In specific a specific embodiment, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0714] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[0715] In a specific embodiment, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0716] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP),

leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[0717] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0718] In a preferred embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[0719] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[0720] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura,

purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[0721] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0722] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0723] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the albumin fusion proteins of the

invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0724] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0725] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0726] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

[0727] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides

encoding albumin fusion proteins of the invention.

[0728] In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a immunosuppressive agent(s).

[0729] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[0730] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0731] Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate IgE concentrations *in vitro* or *in vivo*.

[0732] Moreover, fusion proteins of the invention and/or polynucleotides encoding

albumin fusion proteins of the invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis; myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[0733] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myosititis, myringitis, nephritis, neuritis,

orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0734] In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0735] In other embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[0736] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also directly inhibit the infectious agent

(refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[0737] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance tumor-specific immune responses.

[0738] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[0739] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[0740] In another specific embodiment, the compositions of the invention are used as

an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi.*

[0741] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[0742] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[0743] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[0744] In one embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[0745] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a stimulator of B cell responsiveness to pathogens.

[0746] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an activator of T cells.

[0747] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0748] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to induce higher affinity antibodies.

[0749] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to increase serum immunoglobulin concentrations.

[0750] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0751] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[0752] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full

recovery of B cell populations.

[0753] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be treated (e.g., ameliorated) by administering an albumin fusion protein of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0754] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be treated (e.g., ameliorated) by administering an albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[0755] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention enhance antigen presentation or antagonize antigen presentation *in vitro* or *in vivo*. Moreover, in related embodiments, this enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[0756] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e.,TH2) as opposed to a TH1 cellular response.

[0757] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[0758] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

[0759] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used in the pretreatment of bone marrow samples prior to transplant.

[0760] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[0761] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0762] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[0763] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

[0764] In another specific embodiment, albumin fusion proteins of the invention and/or

polynucleotides encoding albumin fusion proteins of the invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[0765] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[0766] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[0767] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[0768] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[0769] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed to treat idiopathic hyper-

eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[0770] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to enhance or inhibit complement mediated cell lysis.

[0771] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

[0772] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[0773] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be employed to treat adult respiratory distress syndrome (ARDS).

[0774] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to stimulate the regeneration of mucosal surfaces.

[0775] In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies,

HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[0776] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[0777] In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[0778] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[0779] In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[0780] In specific embodiments, the compositions of the invention are used as an agent

to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Blood-Related Disorders

[0781] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[0782] In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0783] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed.

[0784] The fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[0785] The fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to prevent, treat, or diagnose blood dyscrasia.

[0786] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia,

idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune helolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadrugs. Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[0787] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to, major and minor forms of alpha-thalassemia and beta-thalassemia.

[0788] In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome),

hemolytic-uremic syndrome, hemophelias such as hemophelia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorhhagic Telangiectsia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[0789] The effect of the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[0790] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[0791] In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leokocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing,

prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

[0792] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[0793] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited to, lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndome, severe combined immunodeficiency, ataxia telangiectsia).

[0794] The albumin fusion proteins of the invention and/or polynucleotides encoding

albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[0795] In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[0796] In yet another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphpblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukenia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[0797] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[0798] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia,

(including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.

[0799] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as a treatment prior to surgery, to increase blood cell production.

[0800] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

[0801] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[0802] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase cytokine production.

[0803] In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Hyperproliferative Disorders

[0804] In certain embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may proliferate other cells which can inhibit the hyperproliferative disorder.

[0805] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

[0806] Examples of hyperproliferative disorders that can be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0807] Similarly, other hyperproliferative disorders can also be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma,

Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis

Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0808] In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[0809] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous

hyperplasia, and verrucous hyperplasia.

[0810] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[0811] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral

dysplasia, oculodentodigital dysplasia, oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[0812] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[0813] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed.

[0814] In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to, those described herein. In a further preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[0815] Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma,

osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0816] In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[0817] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma,

ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0818] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[0819] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0820] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0821] Another preferred embodiment utilizes polynucleotides encoding albumin fusion proteins of the invention to inhibit aberrant cellular division, by gene therapy using

the present invention, and/or protein fusions or fragments thereof.

[0822] Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide encoding an albumin fusion protein of the present invention, wherein said polynucleotide represses said expression.

[0823] Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the fusion protein of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e., magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e., to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

[0824] Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

[0825] For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art

including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

[0826] The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

[0827] By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

[0828] Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the

effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

[0829] Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference).

[0830] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. These fusion proteins and/or polynucleotides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, these fusion proteins and/or polynucleotides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of these proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

[0831] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering these

albumin fusion proteins and/or polynucleotides, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

[0832] In another embodiment, the invention provides a method of delivering compositions containing the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to targeted cells expressing the a polypeptide bound by, that binds to, or associates with an albumin fusion protein of the invention. Albumin fusion proteins of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[0833] Albumin fusion proteins of the invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the albumin fusion proteins of the invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Cardiovascular Disorders

[0834] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

[0835] Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia,

tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

[0836] Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[0837] Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[0838] Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

[0839] Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis,

pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

[0840] Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[0841] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[0842] Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[0843] Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[0844] Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and

vertebrobasilar insufficiency.

[0845] Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[0846] Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[0847] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Methods of delivering polynucleotides are described in more detail herein.

Respiratory Disorders

[0848] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

[0849] Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis,

tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumoncoccal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

[0850] Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic

granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

[0851] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al., Cell 56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al., Biotech. 9*:630-634 (1991); Folkman *et al., N. Engl. J. Med., 333*:1757-1763 (1995); Auerbach *et al., J. Microvasc. Res. 29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.* Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

[0852] The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid

tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention. For example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[0853] Within yet other aspects, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[0854] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example,

diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

[0855] For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to a hypertrophic scar or keloid.

[0856] Within one embodiment of the present invention fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[0857] Moreover, Ocular disorders associated with neovascularization which can be treated with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al., Am. J. Ophthal.* 85:704-710

(1978) and Gartner *et al., Surv. Ophthal.* 22:291-312 (1978).

[0858] Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (e.g., fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[0859] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[0860] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The

preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

[0861] Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eyes, such that the formation of blood vessels is inhibited.

[0862] Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[0863] Within another aspect of the present invention, methods are provided for

treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

[0864] Additionally, disorders which can be treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[0865] Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

[0866] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization

have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[0867] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[0868] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[0869] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-

angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[0870] Within one aspect of the present invention, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[0871] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0872] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0873] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0874] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate,

sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0875] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, (1992)); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Reproductive System Disorders

[0876] The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the diagnosis, treatment, or

prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[0877] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

[0878] Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodynia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[0879] Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and

prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

[0880] Moreover, diseases and/or disorders of the vas deferens include vasculititis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[0881] Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[0882] Further, the polynucleotides, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

[0883] Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of

congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

[0884] Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[0885] Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[0886] Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism,

Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders,and obstruction of the intestine.

[0887] Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

[0888] Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

[0889] Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Infectious Disease

[0890] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

[0891] Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by albumin fusion proteins of the invention

and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat AIDS.

[0892] Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi:

Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthrasis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium dificile*, *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diptheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae and Mycobacterium tuberculosis)*, Vibrio (e.g., *Vibrio cholerae)*, Neisseriaceae (e.g., *Neisseria gonorrhea*, *Neisseria meningitidis*), Pasteurellacea, Proteus, Pseudomonas (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningiococcus, Pneumococcus and Streptococcus (e.g., *Streptococcus pneumoniae* and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., mengitis types A and B), chlamydia, syphillis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted

diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat: tetanus, diptheria, botulism, and/or meningitis type B.

[0893] Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardias, Helminthiasis, Leishmaniasis, Schistisoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparium*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat, prevent, and/or diagnose malaria.

[0894] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could either be by administering an effective amount of an albumin fusion protein of the invention to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Chemotaxis

[0895] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[0896] Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

[0897] It is also contemplated that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an inhibitor of chemotaxis.

Binding Activity

[0898] Albumin fusion proteins of the invention may be used to screen for molecules that bind to the Therapeutic protein portion of the fusion protein or for molecules to which the Therapeutic protein portion of the fusion protein binds. The binding of the fusion protein and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the fusion protein or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

[0899] Preferably, the molecule is closely related to the natural ligand of the Therapeutic protein portion of the fusion protein of the invention, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et

al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the Therapeutic protein portion of an albumin fusion protein of the invention binds, or at least, a fragment of the receptor capable of being bound by the Therapeutic protein portion of an albumin fusion protein of the invention (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[0900] Preferably, the screening for these molecules involves producing appropriate cells which express the albumin fusion proteins of the invention. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli.*

[0901] The assay may simply test binding of a candidate compound to an albumin fusion protein of the invention, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the fusion protein.

[0902] Alternatively, the assay can be carried out using cell-free preparations, fusion protein/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing an albumin fusion protein, measuring fusion protein/molecule activity or binding, and comparing the fusion protein/molecule activity or binding to a standard.

[0903] Preferably, an ELISA assay can measure fusion protein level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure fusion protein level or activity by either binding, directly or indirectly, to the albumin fusion protein or by competing with the albumin fusion protein for a substrate.

[0904] Additionally, the receptor to which a Therapeutic protein portion of an albumin fusion protein of the invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, in cases wherein the Therapeutic protein portion of the fusion protein corresponds to FGF, expression cloning may be employed wherein polyadenylated RNA is prepared from a cell responsive to the albumin fusion protein, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not

responsive to the albumin fusion protein. Transfected cells which are grown on glass slides are exposed to the albumin fusion protein of the present invention, after they have been labeled. The albumin fusion proteins can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[0905] Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[0906] As an alternative approach for receptor identification, a labeled albumin fusion protein can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule for the Therapeutic protein component of an albumin fusion protein of the invention, the linked material may be resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the fusion protein can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[0907] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the fusion protein, and/or Therapeutic protein portion or albumin component of an albumin fusion protein of the present invention, thereby effectively generating agonists and antagonists of an albumin fusion protein of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides encoding albumin fusion proteins of the invention and thus, the albumin fusion proteins encoded thereby, may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another

embodiment, polynucleotides encoding albumin fusion proteins of the invention and thus, the albumin fusion proteins encoded thereby, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of an albumin fusion protein of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[0908] Other preferred fragments are biologically active fragments of the Therapeutic protein portion and/or albumin component of the albumin fusion proteins of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of a Therapeutic protein portion and/or albumin component of the albumin fusion proteins of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0909] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of an albumin fusion protein of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, an albumin fusion protein of the present invention, and the compound to be screened and ^{3}[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ^{3}[H] thymidine in each case. The amount of fibroblast cell proliferation is

measured by liquid scintillation chromatography which measures the incorporation of ^{3}[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[0910] In another method, a mammalian cell or membrane preparation expressing a receptor for the Therapeutic protein component of a fusion protein of the invention is incubated with a labeled fusion protein of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential fusion protein. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[0911] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the fusion protein/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the albumin fusion proteins of the invention from suitably manipulated cells or tissues.

[0912] Therefore, the invention includes a method of identifying compounds which bind to an albumin fusion protein of the invention comprising the steps of: (a) incubating a candidate binding compound with an albumin fusion protein of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with an albumin fusion protein of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the fusion protein has been altered.

Targeted Delivery

[0913] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a component of an albumin fusion protein of the invention.

[0914] As discussed herein, fusion proteins of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering fusion proteins of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a Therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0915] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering an albumin fusion protein of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[0916] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

[0917] Further contemplated is the use of the albumin fusion proteins of the present invention, or the polynucleotides encoding these fusion proteins, to screen for molecules which modify the activities of the albumin fusion protein of the present invention or proteins corresponding to the Therapeutic protein portion of the albumin fusion protein. Such a method would include contacting the fusion protein with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of the fusion protein following binding.

[0918] This invention is particularly useful for screening therapeutic compounds by using the albumin fusion proteins of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The albumin fusion protein employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the albumin fusion protein. Drugs are screened against such transformed cells or supernatants obtained from culturing such cells, in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and an albumin fusion protein of the present invention.

[0919] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the albumin fusion proteins of the present invention. These methods comprise contacting such an agent with an albumin fusion protein of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the albumin fusion protein or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the albumin fusion protein of the present invention.

[0920] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to an albumin fusion protein of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein.

Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with an albumin fusion protein of the present invention and washed. Bound peptides are then detected by methods well known in the art. Purified albumin fusion protein may be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[0921] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding an albumin fusion protein of the present invention specifically compete with a test compound for binding to the albumin fusion protein or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with an albumin fusion protein of the invention.

Binding Peptides and Other Molecules

[0922] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind albumin fusion proteins of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the albumin fusion proteins of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[0923] This method comprises the steps of:

(a) contacting an albumin fusion protein of the invention with a plurality of molecules; and

(b) identifying a molecule that binds the albumin fusion protein.

[0924] The step of contacting the albumin fusion protein of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the albumin fusion protein on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized albumin fusion protein of the invention. The

molecules having a selective affinity for the albumin fusion protein can then be purified by affinity selection. The nature of the solid support, process for attachment of the albumin fusion protein to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

[0925] Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by an albumin fusion protein of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the albumin fusion protein and the individual clone. Prior to contacting the albumin fusion protein with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for an albumin fusion protein of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for an albumin fusion protein of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

[0926] In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of an albumin fusion protein of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the albumin fusion protein of the invention or the plurality of polypeptides are bound to a solid support.

[0927] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind an albumin fusion protein of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and *in vitro* translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., Science 251:767-773 (1991); Houghten et al., Nature 354:84-86 (1991); Lam et al., Nature 354:82-84 (1991); Medynski, Bio/Technology 12:709-710 (1994); Gallop et al., J. Medicinal Chemistry 37(9):1233-1251 (1994); Ohlmeyer et al., Proc. Natl. Acad. Sci. USA 90:10922-10926 (1993); Erb et al., Proc. Natl. Acad. Sci. USA 91:11422-11426 (1994); Houghten et al., Biotechniques 13:412 (1992); Jayawickreme et al., Proc. Natl. Acad. Sci. USA 91:1614-1618 (1994); Salmon et al., Proc. Natl. Acad. Sci. USA 90:11708-11712 (1993); PCT Publication No. WO 93/20242; and Brenner and Lerner, Proc. Natl. Acad. Sci. USA 89:5381-5383 (1992).

[0928] Examples of phage display libraries are described in Scott et al., Science 249:386-390 (1990); Devlin et al., Science, 249:404-406 (1990); Christian et al., 1992, J. Mol. Biol. 227:711-718 1992); Lenstra, J. Immunol. Meth. 152:149-157 (1992); Kay et al., Gene 128:59-65 (1993); and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

[0929] *In vitro* translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., Proc. Natl. Acad. Sci. USA 91:9022-9026 (1994).

[0930] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., Proc. Natl. Acad. Sci. USA 91:4708-4712 (1994)) can be adapted for use. Peptoid libraries (Simon et al., Proc. Natl. Acad. Sci. USA 89:9367-9371 (1992)) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (Proc. Natl. Acad. Sci. USA 91:11138-11142 (1994)).

[0931] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke (Bio/Technology 13:351-360 (1995) list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-

mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

[0932] Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

[0933] Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[0934] Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley et al., Adv. Exp. Med. Biol. 251:215-218 (1989); Scott et al,. Science 249:386-390 (1990); Fowlkes et al., BioTechniques 13:422-427 (1992); Oldenburg et al., Proc. Natl. Acad. Sci. USA 89:5393-5397 (1992); Yu et al., Cell 76:933-945 (1994); Staudt et al., Science 241:577-580 (1988); Bock et al., Nature 355:564-566 (1992); Tuerk et al., Proc. Natl. Acad. Sci. USA 89:6988-6992 (1992); Ellington et al., Nature 355:850-852 (1992); U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar et al., Science 263:671-673 (1993); and PCT Publication No. WO 94/18318.

[0935] In a specific embodiment, screening to identify a molecule that binds an albumin fusion protein of the invention can be carried out by contacting the library members with an albumin fusion protein of the invention immobilized on a solid phase and harvesting those library members that bind to the albumin fusion protein. Examples of such screening methods, termed "panning" techniques are described by way of example in

Parmley et al., Gene 73:305-318 (1988); Fowlkes et al., BioTechniques 13:422-427 (1992); PCT Publication No. WO 94/18318; and in references cited herein.

[0936] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields et al., Nature 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA 88:9578-9582 (1991) can be used to identify molecules that specifically bind to polypeptides of the invention.

[0937] Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

[0938] Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

[0939] As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

[0940] The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Other Activities

[0941] An albumin fusion protein of the invention and/or polynucleotide encoding an

albumin fusion protein of the invention, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[0942] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[0943] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[0944] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

[0945] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, an albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[0946] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. An albumin fusion

protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[0947] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[0948] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, an albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[0949] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[0950] An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[0951] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

[0952] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of

illustration and are not intended as limiting.

[0953] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the alterations detected in the present invention and practice the claimed methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLES

Example 1: Generation Of pScNCHSA And pScCHSA

[0954] The vectors pScNHSA (ATCC Deposit No. PTA-3279) and pScCHSA (ATCC Deposit No. PTA-3276) are derivatives of pPPC0005 (ATCC Deposit No. PTA-3278) and are used as cloning vectors into which polynucleotides encoding a therapeutic protein or fragment or variant thereof is inserted adjacent to and in translation frame with polynucleotides encoding human serum albumin "HSA". pScCHSA may be used for generating Therapeutic protein-HSA fusions, while pScNHSA may be used to generate HSA-Therapeutic protein fusions.

Generation of pScCHSA: albumin fusion with the albumin moiety C-terminal to the therapeutic portion.

[0955] A vector to facilitate cloning DNA encoding a Therapeutic protein N-terminal to DNA encoding the mature albumin protein was made by altering the nucleic acid sequence that encodes the chimeric HSA signal peptide in pPPC0005 to include the *Xho* I and *Cla* I restriction sites.

[0956] First, the *Xho* I and *Cla* I sites inherent to pPPC0005 (located 3' of the ADH1 terminator sequence) were eliminated by digesting pPPC0005 with *Xho* I and *Cla* I, filling in the sticky ends with T4 DNA polymerase, and religating the blunt ends to create pPPC0006.

[0957] Second, the *Xho* I and *Cla* I restriction sites were engineered into the nucleic acid sequence that encodes the signal peptide of HSA (a chimera of the HSA leader and a kex2 site from mating factor alpha, "MAF") in pPPC0006 using two rounds of PCR. In

the first round of PCR, amplification with primers shown as SEQ ID NO:328 and SEQ ID NO:329 was performed. The primer whose sequence is shown as SEQ ID NO:328 comprises a nucleic acid sequence that encodes part of the signal peptide sequence of HSA, a kex2 site from the mating factor alpha leader sequence, and part of the amino-terminus of the mature form of HSA. Four point mutations were introduced in the sequence, creating the *Xho* I and *Cla* I sites found at the junction of the chimeric signal peptide and the mature form of HSA. These four mutations are underlined in the sequence shown below. In pPPC0005 the nucleotides at these four positions from 5' to 3' are T, G, T, and G.

5'-GCCTCGAGAAAAGAGATGCACACAAGAGTGAGGTTGCTCATCGATTTAAAG ATTTGGG-3' (SEQ ID NO:328) and

5'-AATCGATGAGCAACCTCACTCTTGTGTGCATCTCTTTTCTCGAGGCTCCTGG AATAAGC-3' (SEQ ID NO:329).

A second round of PCR was then performed with an upstream flanking primer, 5'-TACAAACTTAAGAGTCCAATTAGC-3' (SEQ ID NO:330) and a downstream flanking primer 5'-CACTTCTCTAGAGTGGTTTCATATGTCTT-3' (SEQ ID NO:331). The resulting PCR product was then purified and digested with *Afl* II and *Xba* I and ligated into the same sites in pPPC0006 creating pScCHSA. The resulting plasmid has *Xho* I and *Cla* I sites engineered into the signal sequence. The presence of the *Xho* I site creates a single amino acid change in the end of the signal sequence from LDKR to LEKR. The D to E change will not be present in the final albumin fusion protein expression plasmid when a nucleic acid sequence comprising a polynucleotide encoding the Therapeutic portion of the albumin fusion protein with a 5' *Sal* I site (which is compatible with the *Xho* I site) and a 3' *Cla* I site is ligated into the *Xho* I and *Cla* I sites of pScCHSA. Ligation of *Sal* I to *Xho* I restores the original amino acid sequence of the signal peptide sequence. DNA encoding the Therapeutic portion of the albumin fusion protein may be inserted after the Kex2 site (Kex2 cleaves after the dibasic amino acid sequence KR at the end of the signal peptide) and prior to the *Cla* I site.

Generation of pScNHSA: albumin fusion with the albumin moiety N-terminal to the therapeutic portion.

[0958] A vector to facilitate cloning DNA encoding a Therapeutic protein portion C-

terminal to DNA encoding the mature albumin protein, was made by adding three, eight-base-pair restriction sites to pScCHSA. The *Asc* I, *Fse* I, and *Pme* I restriction sites were added in between the *Bsu36* I and *Hind* III sites at the end of the nucleic acid sequence encoding the mature HSA protein. This was accomplished through the use of two complementary synthetic primers containing the *Asc* I, *Fse* I, and *Pme* I restriction sites underlined (SEQ ID NO:332 and SEQ ID NO:333).

5'-AAGCTGCCTTAGGCTTATAATAAGGCGCGCCGGCCGGCCGTTTAAACTAAG CTTAATTCT-3' (SEQ ID NO:332) and

5'-AGAATTAAGCTTAGTTTAAACGGCCGGCCGGCGCGCCTTATTATAAGCCTA AGGCAGCTT-3' (SEQ ID NO:334). These primers were annealed and digested with *Bsu36* I and *Hind* III and ligated into the same sites in pScCHSA creating pScNHSA.

Example 2: General Construct Generation For Yeast Transformation

[0959] The vectors pScNHSA and pScCHSA may be used as cloning vectors into which polynucleotides encoding a therapeutic protein or fragment or variant thereof is inserted adjacent to polynucleotides encoding mature human serum albumin "HSA". pScCHSA is used for generating Therapeutic protein-HSA fusions, while pScNHSA may be used to generate HSA-Therapeutic protein fusions.

Generation of albumin fusion constructs comprising HSA-Therapeutic protein fusion products.

[0960] DNA encoding a Therapeutic protein (e.g., sequences shown in SEQ ID NO:X or known in the art) may be PCR amplified using the primers which facilitate the generation of a fusion construct (e.g., by adding restriction sites, encoding seamless fusions, encoding linker sequences, etc.) For example, one skilled in the art could design a 5' primer that adds polynucleotides encoding the last four amino acids of the mature form of HSA (and containing the *Bsu*36I site) onto the 5' end of DNA encoding a Therapeutic protein; and a 3' primer that adds a STOP codon and appropriate cloning sites onto the 3' end of the Therapeutic protein coding sequence. For instance, the forward primer used to amplify DNA encoding a Therapeutic protein might have the sequence, 5'-aagctGCCTTAGGCTTA$(N)_{15}$-3' (SEQ ID NO:334) where the underlined sequence is a *Bsu*36I site, the upper case nucleotides encode the last four amino acids of the mature

HSA protein (ALGL), and $(N)_{15}$ is identical to the first 15 nucleotides encoding the Therapeutic protein of interest. Similarly, the reverse primer used to amplify DNA encoding a Therapeutic protein might have the sequence, 5'-GCGCGC*GTTTAAAC*GGCCGGCCGGCGCGCCTTATTA$(N)_{15}$-3' (SEQ ID NO:335) where the italicized sequence is a *Pme* I site, the double underlined sequence is an *Fse* I site, the singly underlined sequence is an *Asc* I site, the boxed nucleotides are the reverse complement of two tandem stop codons, and $(N)_{15}$ is identical to the reverse complement of the last 15 nucleotides encoding the Therapeutic protein of interest. Once the PCR product is amplified it may be cut with *Bsu*36I and one of (*Asc* I, *Fse* I, or *Pme* I) and ligated into pScNHSA.

[0961] The presence of the *Xho* I site in the HSA chimeric leader sequence creates a single amino acid change in the end of the chimeric signal sequence, i.e. the HSA-kex2 signal sequence, from LDKR to LEKR.

Generation of albumin fusion constructs comprising gene-HSA fusion products.

[0962] Similar to the method described above, DNA encoding a Therapeutic protein may be PCR amplified using the following primers: A 5' primer that adds polynucleotides containing a *Sal* I site and encoding the last three amino acids of the HSA leader sequence, DKR, onto the 5' end of DNA encoding a Therapeutic protein; and a 3' primer that adds polynucleotides encoding the first few amino acids of the mature HSA containing a *Cla* I site onto the 3' end of DNA encoding a Therapeutic protein. For instance, the forward primer used to amplify the DNA encoding a Therapeutic protein might have the sequence, 5'-aggagcgtcGACAAAAGA$(N)_{15}$-3' (SEQ ID NO:336) where the underlined sequence is a *Sal* I site, the upper case nucleotides encode the last three amino acids of the HSA leader sequence (DKR), and $(N)_{15}$ is identical to the first 15 nucleotides encoding the Therapeutic protein of interest. Similarly, the reverse primer used to amplify the DNA encoding a Therapeutic protein might have the sequence, 5'-CTTTAA*ATCGAT*GAGCAACCTCACTCTTGTGTGCATC$(N)_{15}$-3' (SEQ ID NO:337) where the italicized sequence is a *Cla* I site, the underlined nucleotides are the reverse complement of the DNA encoding the first 9 amino acids of the mature form of HSA (DAHKSEVAH, SEQ ID NO:391), and $(N)_{15}$ is identical to the reverse complement of the last 15 nucleotides encoding the Therapeutic protein of interest. Once the PCR product is

amplified it may be cut with *Sal* I and *Cla* I and ligated into pScCHSA digested with *Xho* I and *Cla* I. A different signal or leader sequence may be desired, for example, invertase "INV" (Swiss-Prot Accession P00724), mating factor alpha "MAF" (Genbank Accession AAA18405), MPIF (Geneseq AAF82936), Fibulin B (Swiss-Prot Accession P23142), Clusterin (Swiss-Prot Accession P10909), Insulin-Like Growth Factor- Binding Protein 4 (Swiss-Prot Accession P22692), and permutations of the HSA leader sequence can be subcloned into the appropriate vector by means of standard methods known in the art.

Generation of albumin fusion construct compatible for expression in yeast S. cerevisiae.

[0963] The *Not* I fragment containing the DNA encoding either an N-terminal or C-terminal albumin fusion protein generated from pScNHSA or pScCHSA may then be cloned into the *Not* I site of pSAC35 which has a LEU2 selectable marker. The resulting vector is then used in transformation of a yeast *S. cerevisiae* expression system.

EXAMPLE 3: General Expression In Yeast *S. Cerevisiae*

[0964] An expression vector compatible with yeast expression can be transformed into yeast *S. cerevisiae* by lithium acetate transformation, electroporation, or other methods known in the art and or as described in part in Sambrook, Fritsch, and Maniatis. (1989). "Molecular Cloning: A Laboratory Manual, 2nd edition", volumes 1-3, and in Ausubel et al. (2000). Massachusetts General Hospital and Harvard Medical School "Current Protocols in Molecular Biology", volumes 1-4. The expression vectors are introduced into *S. cerevisiae* strains DXY1, D88, or BXP10 by transformation, individual transformants can be grown, for example, for 3 days at 30°C in 10 mL YEPD (1% w/v yeast extract, 2 % w/v, peptone, 2 % w/v, dextrose), and cells can be collected at stationary phase after 60 hours of growth. Supernatants are collected by clarifying cells at 3000g for 10 minutes.

[0965] pSAC35 (Sleep et al., Biotechnology 8:42 (1990) and see Figure 4) comprises, in addition to the LEU2 selectable marker, the entire yeast 2 μm plasmid to provide replication functions, the PRB1 promoter, and the ADH1 termination signal.

EXAMPLE 4: General Purification Of An Albumin Fusion Protein Expressed From An Albumin Fusion In Yeast *S. Cerevisiae*

[0966] In preferred embodiments, albumin fusion proteins of the invention comprise

the mature form of HSA fused to either the N- or C- terminus of the mature form of a therapeutic protein or portions thereof (e.g., the mature form of a therapeutic protein listed in Table 1, or the mature form of a therapeutic protein shown in Table 2 as SEQ ID NO:Z). In one embodiment of the invention, albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature albumin fusion protein is secreted directly into the culture medium. Albumin fusion proteins of the invention preferably comprise heterologous signal sequences (e.g., the non-native signal sequence of a particular therapeutic protein) including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In preferred embodiments, the fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[0967] Albumin fusion proteins expressed in yeast as described above can be purified on a small-scale over a Dyax peptide affinity column as follows. Supernatants from yeast expressing an albumin fusion protein is diafiltrated against 3 mM phosphate buffer pH 6.2, 20 mM NaCl and 0.01% Tween 20 to reduce the volume and to remove the pigments. The solution is then filtered through a 0.22 μm device. The filtrate is loaded onto a Dyax peptide affinity column. The column is eluted with 100 mM Tris/HCl, pH 8.2 buffer. The peak fractions containing protein are collected and analyzed on SDS-PAGE after concentrating 5-fold.

[0968] For large scale purification, the following method can be utilized. The supernatant in excess of 2 L is diafiltered and concentrated to 500 mL in 20 mM Tris/HCl pH 8.0. The concentrated protein solution is loaded onto a pre-equilibrated 50 mL DEAE-Sepharose Fast Flow column, the column is washed, and the protein is eluted with a linear gradient of NaCl from 0 to 0.4 M NaCl in 20 mM Tris/HCl, pH 8.0. Those fractions containing the protein are pooled, adjusted to pH 6.8 with 0.5 M sodium phosphate (NaH_2PO_4). A final concentration of 0.9 M $(NH_4)_2SO_4$ is added to the protein solution and

the whole solution is loaded onto a pre-equilibrated 50 mL Butyl650S column. The protein is eluted with a linear gradient of ammonium sulfate (0.9 to 0 M $(NH_4)_2SO_4$). Those fractions with the albumin fusion are again pooled, diafiltered against 10 mM Na_2HPO_4/citric acid buffer pH 5.75, and loaded onto a 50 mL pre-equilibrated SP-Sepharose Fast Flow column. The protein is eluted with a NaCl linear gradient from 0 to 0.5 M. The fractions containing the protein of interest are combined, the buffer is changed to 10 mM Na_2HPO_4/citric acid pH 6.25 with an Amicon concentrator, the conductivity is < 2.5 mS/cm. This protein solution is loaded onto a 15 mL pre-equilibrated Q-Sepharose high performance column, the column is washed, and the protein is eluted with a NaCl linear gradient from 0 to 0.15 M NaCl. The purified protein can then be formulated into a specific buffer composition by buffer exchange.

Example 5: General Construct Generation For Mammalian Cell Transfection

Generation of albumin fusion construct compatible for expression in mammalian cell-lines.

[0969] Albumin fusion constructs can be generated in expression vectors for use in mammalian cell culture systems: DNA encoding a therapeutic protein can be cloned N-terminus or C-terminus to HSA in a mammalian expression vector by standard methods known in the art (e.g., PCR amplification, restriction digestion, and ligation). Once the expression vector has been constructed, transfection into a mammalian expression system can proceed. Suitable vectors are known in the art including, but not limited to, for example, the pC4 vector, and/or vectors available from Lonza Biologics, Inc. (Portsmouth, NH).

[0970] The DNA encoding human serum albumin has been cloned into the pC4 vector which is suitable for mammalian culture systems, creating plasmid pC4:HSA (ATCC Deposit # PTA-3277). This vector has a DiHydroFolate Reductase, "DHFR", gene that will allow for selection in the presence of methotrexate.

[0971] The pC4:HSA vector is suitable for expression of albumin fusion proteins in CHO cells. For expression, in other mammalian cell culture systems, it may be desirable to subclone a fragment comprising, or alternatively consisting of, DNA which encodes for an albumin fusion protein into an alternative expression vector. For example, a fragment

comprising, or alternatively consisting, of DNA which encodes for a mature albumin fusion protein may be subcloned into another expression vector including, but not limited to, any of the mammalian expression vectors described herein.

[0972] In a preferred embodiment, DNA encoding an albumin fusion construct is subcloned into vectors provided by Lonza Biologics, Inc. (Portsmouth, NH) by procedures known in the art for expression in NS0 cells.

Generation of albumin fusion constructs comprising HSA-Therapeutic Protein fusion products.

[0973] Using pC4:HSA (ATCC Deposit # PTA-3277), albumin fusion constructs can be generated in which the Therapeutic protein portion is C terminal to the mature albumin sequence. For example, one can clone DNA encoding a Therapeutic protein of fragment or variant thereof between the *Bsu* 36I and *Asc* I restriction sites of the vector. When cloning into the *Bsu* 36I and *Asc* I, the same primer design used to clone into the yeast vector system (SEQ ID NO:334 and 335) may be employed (see Example 2).

Generation of albumin fusion constructs comprising gene-HSA fusion products.

[0974] Using pC4:HSA (ATCC Deposit # PTA-3277), albumin fusion constructs can be generated in which a Therapeutic protein portion is cloned N terminal to the mature albumin sequence. For example, one can clone DNA encoding a Therapeutic protein that has its own signal sequence between the *Bam* HI (or *Hind* III) and *Cla* I sites of pC4:HSA. When cloning into either the *Bam* HI or *Hind* III site, it is preferable to include a Kozak sequence (**CCGCCACCATG**, SEQ ID NO:392) prior to the translational start codon of the DNA encoding the Therapeutic protein. If a Therapeutic protein does not have a signal sequence, DNA encoding that Therapeutic protein may be cloned in between the *Xho* I and *Cla* I sites of pC4:HSA. When using the *Xho* I site, the following 5' (SEQ ID NO:338) and 3' (SEQ ID NO:339) exemplary PCR primers may be used:

5'-**CCGCCGCTCGAGGGGTGTGTTTCGTCGA(N)$_{18}$-3'** (SEQ ID NO:338); and

5'-**AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATC(N)$_{18}$-3'** (SEQ ID NO:339).

[0975] In the 5' primer (SEQ ID NO:338), the underlined sequence is a *Xho* I site; and the *Xho* I site and the DNA following the *Xho* I site code for the last seven amino acids of the leader sequence of natural human serum albumin. In SEQ ID NO:338, "$(N)_{18}$" is DNA

identical to the first 18 nucleotides encoding the Therapeutic protein of interest. In the 3' primer (SEQ ID NO:339), the underlined sequence is a *Cla* I site; and the *Cla* I site and the DNA following it are the reverse complement of the DNA encoding the first 10 amino acids of the mature HSA protein (SEQ ID NO:327). In SEQ ID NO:339 "$(N)_{18}$" is the reverse complement of DNA encoding the last 18 nucleotides encoding the Therapeutic protein of interest. Using these two primers, one may PCR amplify the Therapeutic protein of interest, purify the PCR product, digest it with *Xho* I and *Cla* I restriction enzymes and clone it into the *Xho* I and *Cla* I sites in the pC4:HSA vector.

[0976] If an alternative leader sequence is desired, the native albumin leader sequence can be replaced with the chimeric albumin leader, i.e., the HSA-kex2 signal peptide, or an alternative leader by standard methods known in the art. (For example, one skilled in the art could routinely PCR amplify an alternate leader and subclone the PCR product into an albumin fusion construct in place of the albumin leader while maintaining the reading frame).

EXAMPLE 6: General Expression In Mammalian Cell-Lines

[0977] An albumin fusion construct generated in an expression vector compatible with expression in mammalian cell-lines can be transfected into appropriate cell-lines by calcium phosphate precipitation, lipofectamine, electroporation, or other transfection methods known in the art and/or as described in Sambrook, Fritsch, and Maniatis. 1989. "Molecular Cloning: A Laboratory Manual, 2nd edition" and in Ausubel et al. 2000. Massachusetts General Hospital and Harvard Medical School "Current Protocols in Molecular Biology", volumes 1-4. The transfected cells are then selected for by the presence of a selecting agent determined by the selectable marker in the expression vector.

[0978] The pC4 expression vector (ATCC Accession No. 209646) is a derivative of the plasmid pSV2-DHFR (ATCC Accession No. 37146). pC4 contains the strong promoter Long Terminal Repeats "LTR" of the Rous Sarcoma Virus (Cullen et al., March 1985, Molecular and Cellular Biology, 438-447) and a fragment of the CytoMegaloVirus "CMV"-enhancer (Boshart et al., Cell 41: 521-530 (1985)). The vector also contains the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary

"CHO" cells or other cell-lines lacking an active DHFR gene are used for transfection. Transfection of an albumin fusion construct in pC4 into CHO cells by methods known in the art will allow for the expression of the albumin fusion protein in CHO cells, followed by leader sequence cleavage, and secretion into the supernatant. The albumin fusion protein is then further purified from the supernatant.

[0979] The pEE12.1 expression vector is provided by Lonza Biologics, Inc. (Portsmouth, NH) and is a derivative of pEE6 (Stephens and Cockett, Nucl. Acids Res. 17: 7110 (1989)). This vector comprises a promoter, enhancer and complete 5'-untranslated region of the Major Immediate Early gene of the human CytoMegaloVirus, "hCMV-MIE" (International Publication # WO89/01036), upstream of a sequence of interest, and a Glutamine Synthetase gene (Murphy et al., Biochem J. 227: 277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992); US patent US 5,122,464) for purposes of selection of transfected cells in selective methionine sulphoximine containing medium. Transfection of albumin fusion constructs made in pEE12.1 into NS0 cells (International Publication # WO86/05807) by methods known in the art will allow for the expression of the albumin fusion protein in NS0 cells, followed by leader sequence cleavage, and secretion into the supernatant. The albumin fusion protein is then further purified from the supernatant using techniques described herein or otherwise known in the art.

[0980] Expression of an albumin fusion protein may be analyzed, for example, by SDS-PAGE and Western blot, reversed phase HPLC analysis, or other methods known in the art.

[0981] Stable CHO and NS0 cell-lines transfected with albumin fusion constructs are generated by methods known in the art (e.g., lipofectamine transfection) and selected, for example, with 100 nM methotrexate for vectors having the DiHydroFolate Reductase 'DHFR' gene as a selectable marker or through growth in the absence of glutamine. Expression levels can be examined for example, by immunoblotting, primarily, with an anti-HSA serum as the primary antibody, or, secondarily, with serum containing antibodies directed to the Therapeutic protein portion of a given albumin fusion protein as the primary antibody.

[0982] Expression levels are examined by immunoblot detection with anti-HSA serum as the primary antibody. The specific productivity rates are determined via ELISA in which the capture antibody can be a monoclonal antibody towards the therapeutic protein

portion of the albumin fusion and the detecting antibody can be the monoclonal anti-HSA-biotinylated antibody *(or vice versa),* followed by horseradish peroxidase/streptavidin binding and analysis according to the manufacturer's protocol.

Example 7: General Purification Of An Albumin Fusion Protein Expressed From An Albumin Fusion Construct In Mammalian Cell-Lines

[0983] In preferred embodiments, albumin fusion proteins of the invention comprise the mature form of HSA fused to either the N- or C- terminus of the mature form of a therapeutic protein or portions thereof (e.g., the mature form of a therapeutic protein listed in Table 1, or the mature form of a therapeutic protein shown in Table 2 as SEQ ID NO:Z). In one embodiment of the invention, albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature albumin fusion protein is secreted directly into the culture medium. Albumin fusion proteins of the invention preferably comprise heterologous signal sequences (e.g., the non-native signal sequence of a particular therapeutic protein) including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In preferred embodiments, the fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[0984] Albumin fusion proteins from mammalian cell-line supernatants are purified according to different protocols depending on the expression system used.

Purification from CHO and 293T cell-lines.

[0985] Purification of an albumin fusion protein from CHO cell supernatant or from transiently transfected 293T cell supernatant may involve initial capture with an anionic HQ resin using a sodium phosphate buffer and a phosphate gradient elution, followed by affinity chromatography on a Blue Sepharose FF column using a salt gradient elution. Blue Sepharose FF removes the main BSA/fetuin contaminants. Further purification over

the Poros PI 50 resin with a phosphate gradient may remove and lower endotoxin contamination as well as concentrate the albumin fusion protein.

Purification from NS0 cell-line.

[0986] Purification of an albumin-fusion protein from NS0 cell supernatant may involve Q-Sepharose anion exchange chromatography, followed by SP-sepharose purification with a step elution, followed by Phenyl-650M purification with a step elution, and, ultimately, diafiltration.

[0987] The purified protein may then be formulated by buffer exchange.

Example 8: Construct Id 2448, Glp1-Hsa, Generation.

[0988] Construct ID 2448, pSAC35:GLP1.H98-R127.HSA, encodes for a GLP1-HSA fusion protein which comprises the HSA chimeric leader sequence, i.e. the HSA-kex2 signal peptide, the mature GLP1 protein, i.e. H98-R127, fused to the amino-terminus of the mature form of HSA cloned into the *S. cerevisiae* yeast expression vector pSAC35.

Cloning of GLP1 cDNA for construct 2448

[0989] The DNA encoding the mature form of GLP1 was codon optimized so as not to hybridize to the wild-type DNA encoding the mature form of GLP1. The polynucleotide encoding the codon optimized GLP1 was generated with two overlapping primers GLP1-1 and GLP1-2, described below, with optimal codon usage for yeast *S. cerevisiae*, cut with SalI/ClaI, and ligated into XhoI/ClaI cut pScCHSA. After sequence confirmation, the NotI fragment encompassing the GLP1 albumin fusion was subcloned into pSAC35. Construct ID #2448 encodes an albumin fusion protein containing the chimeric leader sequence of HSA, the mature form of GLP1, followed by the mature HSA protein (SEQ ID NO:327).

[0990] Two overlapping oligonucleotides suitable for synthesis of the polynucleotide encoding the mature form of GLP1, GLP1-1 and GLP1-2, are:

GLP1-1:5'-AGGAGC*GTCGAC*AAAAGA**CACGCTGAAGGTACTTTCACTTCTGATGTTTCT TCTTACTTGGAAGGTCAAGCTGCTAAGGAATTCATTGCT**-3' (SEQ ID NO:312)

GLP1-2:5'-CTTTAA*ATCGAT*GAGCAACCTCACTCTTGTGTGCATCTCTACCCTTAACCAACC **AAGCAATGAATTCCTTAGCAG** –3' (SEQ ID NO:313)

GLP1-1 incorporates a SalI cloning site (shown in italics) and the DNA encoding the first 24 amino acids (shown in bold) of the ORF of the mature form of GLP1, i.e. His-98 to Ala-121. In GLP1-2, the italicized sequence is a ClaI site; and the ClaI site and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. In GLP1-2, the bolded sequence is the reverse complement of the 38 nucleotides encoding the last 12 amino acid residues Ala-116 to Arg-127 of the mature form of GLP1. Using these two primers, the mature GLP1 protein was generated by annealing, extension of the annealed primers, digestion with SalI and ClaI, and subcloning into XhoI/ClaI digested pScCHSA. The NotI fragment from this clone was then ligated into the NotI site of pSAC35 to generate construct ID 2448. Construct ID #2448 encodes an albumin fusion protein containing the chimeric leader sequence, the mature form of GLP1, i.e. His-98 to Arg-127, and the mature form of HSA.

Expression and Purification of Construct ID 2448.

Expression in yeast S. cerevisiae.

[0991] Construct 2448 was transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[0992] The cell supernatant containing the secreted GLP1-HSA fusion protein expressed from construct ID #2448 in yeast *S. cerevisiae* was purified as described below (also see Example 4). Specifically, the yeast supernatant was equilibrated to pH 7.0 and 2 M NaCl, loaded onto a POROS HP2 resin (phenyl) column, washed with Tris pH 7.0/ 2 M NaCl and eluted with a linear gradient from 2 M to 0 M NaCl at pH 7.0. The albumin fusion eluted with > 1 M NaCl and was ~ 90 % pure. N-terminal sequencing should generate the amino-terminus sequence (i.e. HAEGT) of the mature form of GLP1.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2448.

Method

[0993] The in vitro assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the GLP1 albumin fusion protein encoded by construct 2448 can be carried out

as described below in Example 28.

Result

[0994] At all concentrations including 1 nM, 10 nM, and 100 nM, the GLP1 albumin fusion encoded by construct 2448 demonstrated enhanced glucose uptake by the 3T3-L1 adipocytes and, consequently, greater insulin sensitivity as compared to the GLP1 protein.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2448.

Method

[0995] The in vitro assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the GLP1 albumin fusion protein encoded by construct 2448 can be carried out as described below under heading: "Example 29: In vitro Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2448 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[0996] The activity of the GLP1 albumin fusion protein encoded by construct 2448 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 9: Construct Id 2455, Hsa-Glp1, Generation

[0997] Construct ID 2455, pSAC35:HSA.GLP1.H98-R127, comprises DNA encoding for a GLP1 albumin fusion protein which has the HSA chimeric leader sequence, i.e. the HSA-kex2 signal peptide, followed by the mature form of HSA fused to the amino terminus of the mature form of GLP1, cloned into the *S. cerevisiae* yeast expression vector pSAC35.

Cloning of GLP1 cDNA for construct 2455

[0998] The DNA encoding the mature form of GLP1 was codon optimized so as not to hybridize to the wild-type DNA encoding the mature form of GLP1. The polynucleotide encoding the codon optimized GLP1 was generated with two overlapping primers GLP1-3 and GLP1-4, described below, with optimal codon usage for yeast *S. cerevisiae*, that were annealed, extended, cut with Bsu36I/AscI, and ligated into Bsu36I/AscI cut pScNHSA. After sequence confirmation, the NotI fragment encompassing the GLP1 albumin fusion was subcloned into pSAC35. Construct ID #2455 encodes an albumin fusion protein containing the chimeric leader sequence and mature form of HSA and the mature form of GLP1, His-98 to Arg-127.

[0999] Two overlapping oligonucleotides suitable for synthesis of the polynucleotide encoding the mature form of GLP1, GLP1-3 and GLP1-4, are:

GLP1-3:5'- AAGCTG*CCTTAGG*CTT**ACACGCTGAAGGTACTTTCACTTCTGATGTTTCTTCTT ACTTGGAAGGTCAAGCTGCTAAGGAA TTCATTGCT** -3' (SEQ ID NO:314)

GLP1-4:5'- *GGCGCGCC*T**CATCTACCCTTAACCAACCAAGCAATGAATTCCTTAGCAG** –3' (SEQ ID NO:315)

GLP1-3 incorporates a Bsu36I cloning site (shown in italics) and the DNA encoding the first 24 amino acids (shown in bold) of the ORF of the mature form of GLP1, i.e. His-98 to Ala-121. In GLP1-4, the italicized sequence is an AscI site and the last 38 nucleotides in bold are the reverse complement of DNA encoding the last 12 amino acid residues Ala-116 to Arg-127 of the mature form of GLP1 (for general construct cloning see Example 2). Using these two primers, the mature GLP1 protein was generated by annealing, extension of the annealed primers, digestion with Bsu36I and AscI, and subcloning into Bsu36I/AscI digested pScNHSA. The NotI fragment from this clone was then ligated into the NotI site of pSAC35 to generate construct ID 2455.

Expression and Purification of Construct ID 2455.

Expression yeast S. cerevisiae.

[1000] Construct 2455 was transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1001] The cell supernatant containing the secreted HSA–GLP1 fusion protein

expressed from construct ID #2455 in yeast *S. cerevisiae* was purified as described below (also see Example 4). Specifically, the yeast supernatant was equilibrated to pH 7.0 and 2 M NaCl, loaded onto a POROS HP2 resin (phenyl) column, washed with Tris pH 7.0/ 2 M NaCl and eluted with a linear gradient from 2 M to 0 M NaCl at pH 7.0. The albumin fusion eluted with > 1 M NaCl and was ~ 90 % pure. N-terminal sequencing should generate the amino-terminus sequence (i.e. DAHKS) of the mature form of HSA.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2455.

Method

[1002] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the GLP1 albumin fusion protein encoded by construct 2455 can be carried out as described below in Example 28.

Result

[1003] At all concentrations including 1 nM, 10 nM, and 100 nM, the GLP1 albumin fusion encoded by construct 2455 demonstrated enhanced glucose uptake by the 3T3-L1 adipocytes and, consequently, greater insulin sensitivity as compared to the GLP1 protein.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2455.

Method

[1004] The in vitro assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the GLP1 albumin fusion protein encoded by construct 2455 can be carried out as described below under heading: "Example 29: In vitro Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2455 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1005] The activity of the GLP1 albumin fusion protein encoded by construct 2455 can

be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: In vivo Mouse Model of NIDDM".

Example 10: Construct Id 2456, GLP1-HSA, Generation.

[1006] Construct ID 2456, pSAC35:GLP1.H98-R127.HSA, encodes for a GLP1-HSA fusion protein which comprises the HSA chimeric leader sequence, i.e. the HSA-kex2 signal peptide, the mature GLP1 protein, i.e. H98-R127, with the exception of Ala-99 mutated to Gly, fused to the amino-terminus of the mature form of HSA cloned into the *S. cerevisiae* yeast expression vector pSAC35. Construct ID #2456 is designed to produce a GLP-1 albumin fusion protein that will be resistant to cleavage by Dipeptidyl Peptidase IV, "DP IV" (Hildebrandt et al., Scand J Gastroenterol, 36(10): 1067-72 (2001)), *in vivo*.

Cloning of GLP1 cDNA for construct 2456

[1007] The DNA encoding the mature form of GLP1 was codon optimized so as not to hybridize to the wild-type DNA encoding the mature form of GLP1. The polynucleotide encoding the codon optimized GLP1 was generated with two overlapping primers GLP1-5 and GLP1-6, described below, with optimal codon usage for yeast *S. cerevisiae*, cut with SalI/ClaI, and ligated into XhoI/ClaI cut pScCHSA. After sequence confirmation, the NotI fragment encompassing the GLP1 albumin fusion was subcloned into pSAC35. Construct ID #2456 encodes an albumin fusion protein containing the chimeric leader sequence of HSA, the mature form of GLP1 with the exception of Ala-99 mutated to Gly, followed by the mature HSA protein

[1008] Two overlapping oligonucleotides suitable for synthesis of the polynucleotide encoding the mature form of GLP1, GLP1-5 and GLP1-6, are:

GLP1-5:5'-AGGAGC*GTCGAC*AAAAGACACG**GTGAAGGTACTTTCACTTCTGATGTTTCT TCTTACTTGGAAGGTCAAGCTGCTAAGGAATTCATTGCT**-3' (SEQ ID NO:316)

GLP1-6:5'-CTTTAA*ATCGAT***GAGCAACCTCACTCTTGTGTGCATCTCTACCCTTAACCAACC AAGCAATGAATTCCTTAGCAG**-3' (SEQ ID NO:317)

GLP1-5 incorporates a SalI cloning site (shown in italics) and the DNA encoding the first 24 amino acids (shown in bold) of the ORF of the mature form of GLP1, i.e. His-98 to

Ala-121, with the exception of Ala-99 mutated to Gly. In GLP1-6, the italicized sequence is a ClaI site; and the ClaI site and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. In GLP1-6, the bolded sequence is the reverse complement of the 38 nucleotides encoding the last 12 amino acid residues Ala-116 to Arg-127 of the mature form of GLP1. Using these two primers, the mature GLP1 protein was generated by annealing, extension of the annealed primers, digestion with SalI and ClaI, and subcloning into XhoI/ClaI digested pScCHSA. The NotI fragment from this clone was then ligated into the NotI site of pSAC35 to generate construct ID 2456. Construct ID #2456 encodes an albumin fusion protein containing the chimeric leader sequence, the mature form of GLP1, i.e. His-98 to Arg-127, with the exception of Ala-99 mutated to Gly, and the mature form of HSA.

Expression and Purification of Construct ID 2456.

Expression yeast S. cerevisiae.

[1009] Construct 2456 was transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1010] The cell supernatant containing the secreted GLP1-HSA fusion protein expressed from construct ID #2456 in yeast *S. cerevisiae* was purified as described below (also see Example 4). Specifically, the yeast supernatant was equilibrated to pH 7.0 and 2 M NaCl, loaded onto a POROS HP2 resin (phenyl) column, washed with Tris pH 7.0/ 2 M NaCl and eluted with a linear gradient from 2 M to 0 M NaCl at pH 7.0. N-terminal sequencing should generate the amino-terminus sequence (i.e. HAEGT) of the mature form of GLP1.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2456.

Method

[1011] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the GLP1 albumin fusion protein encoded by construct 2456 can be carried out as described below in Example 28.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2456.

Method

[1012] The in vitro assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the GLP1 albumin fusion protein encoded by construct 2456 can be carried out as described below under heading: "Example 29: In vitro Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2456 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1013] The activity of the GLP1 albumin fusion protein encoded by construct 2456 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 11: Construct ID 2457, HSA-GLP1, Generation.

[1014] Construct ID 2457, pSAC35:HSA.GLP1.H98-R127, comprises DNA encoding for a GLP1 albumin fusion protein which has the HSA chimeric leader sequence, i.e. the HSA-kex2 signal peptide, followed by the mature form of HSA fused to the amino terminus of the mature form of GLP1 with the exception of the Ala-99 to Gly mutation, cloned into the *S. cerevisiae* yeast expression vector pSAC35. Construct ID #2457 is designed to produce a GLP-1 albumin fusion protein that will be resistant to cleavage by Dipeptidyl Peptidase IV, "DP IV" (Hildebrandt et al., Scand J Gastroenterol, 36(10): 1067-72 (2001)), *in vivo*.

Cloning of GLP1 cDNA for construct 2457

[1015] The DNA encoding the mature form of GLP1 was codon optimized so as not to

hybridize to the wild-type DNA encoding the mature form of GLP1. The polynucleotide encoding the codon optimized GLP1 was generated with two overlapping primers GLP1-7 and GLP1-8, described below, with optimal codon usage for yeast *S. cerevisiae*, that were annealed, extended, cut with *Bsu* 36I/*Asc* I, and ligated into *Bsu* 36I/*Asc* I cut pScNHSA. After sequence confirmation, the NotI fragment encompassing the GLP1 albumin fusion with the Ala-99 to Gly mutation was subcloned into pSAC35. Construct ID #2457 encodes an albumin fusion protein containing the chimeric leader sequence and mature form of HSA and the mature form of GLP1, His-98 to Arg-127, with the exception of the Ala-99 to Gly mutation.

[1016] Two overlapping oligonucleotides suitable for synthesis of the polynucleotide encoding the mature form of GLP1, GLP1-7 and GLP1-8, are:

GLP1-7:5'- AAGCTG*CCTTAGG*CTTACACG**GTGAAGGTACTTTCACTTCTGATGTTTCTTCT TACTTGGAAGGTCAAGCTGCTAAGGAA TTCATTGCT** -3' (SEQ ID NO:318)

GLP1-8:5'- *GGCGCGCC*TCATCTACCCTTAACCAACCAAGCAATGAATTCCTTAGCAG –3' (SEQ ID NO:319)

GLP1-7 incorporates a Bsu36I cloning site (shown in italics) and the DNA encoding the first 24 amino acids (shown in bold) of the ORF of the mature form of GLP1, i.e. His-98 to Ala-121 with the exception of the Ala-99 to Gly mutation. In GLP1-8, the italicized sequence is an AscI site and the last 38 nucleotides in bold are the reverse complement of DNA encoding the last 12 amino acid residues of the mature form of GLP1, i.e. Ala-116 to Arg-127 (for general construct cloning see Example 2). Using these two primers, the mature GLP1 protein was generated by annealing, extension of the annealed primers, digestion with *Bsu* 36I and *Asc* I, and subcloning into *Bsu* 36I/*Asc* I digested pScNHSA. The NotI fragment from this clone was then ligated into the NotI site of pSAC35 to generate construct ID 2457.

Expression and Purification of Construct ID 2457.

Expression yeast S. cerevisiae.

[1017] Construct 2457 was transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1018] The cell supernatant containing the secreted HSA–GLP1 fusion protein expressed from construct ID #2457 in yeast *S. cerevisiae* was purified as described below (also see Example 4). Specifically, the yeast supernatant was equilibrated to pH 7.0 and 2 M NaCl, loaded onto a POROS HP2 resin (phenyl) column, washed with Tris pH 7.0/ 2 M NaCl and eluted with a linear gradient from 2 M to 0 M NaCl at pH 7.0. N-terminal sequencing should generate the amino-terminus sequence (i.e. DAHKS) of the mature form of HSA.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2457.

Method

[1019] The in vitro assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the GLP1 albumin fusion protein encoded by construct 2457 can be carried out as described below in Example 28.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2457.

Method

[1020] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the GLP1 albumin fusion protein encoded by construct 2457 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2457 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1021] The activity of the GLP1 albumin fusion protein encoded by construct 2457 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32:

Histological Examination of NOD Mice", and "Example 34: In vivo Mouse Model of NIDDM".

Example 12: Construct ID 2470, Exendin-4-HSA, Generation

[1022] Construct ID 2470, pSAC35:exendin.H48-S86.HSA, encodes for an EXENDIN4-HSA fusion protein which comprises the HSA chimeric leader sequence, i.e. the HSA-kex2 signal peptide, the mature EXENDIN4 protein, i.e. H48-S86, fused to the amino-terminus of the mature form of HSA cloned into the *S. cerevisiae* yeast expression vector pSAC35.

Cloning of EXENDIN4 cDNA for construct 2470

[1023] The DNA encoding the mature form of EXENDIN4 was codon optimized so as not to hybridize to the wild-type DNA encoding the mature form of EXENDIN4. The polynucleotide encoding the codon optimized EXENDIN4 was generated with four overlapping primers EXTC-1, EXTC-2, EXTC-3, and EXTC-4 described below, with optimal codon usage for yeast *S. cerevisiae*, cut with SalI/ClaI, and ligated into XhoI/ClaI cut pScCHSA. After sequence confirmation, the NotI fragment encompassing the EXENDIN4 albumin fusion was subcloned into pSAC35. Construct ID #2470 encodes an albumin fusion protein containing the chimeric leader sequence of HSA, the mature form of EXENDIN4, followed by the mature HSA protein.

[1024] Four overlapping oligonucleotides suitable for synthesis of the polynucleotide encoding the mature form of EXENDIN4, EXTC-1, EXTC-2, EXTC-3, and EXTC-4, are:

EXTC-1: 5'- TCCAGGAGC*GTCGAC*AAAAGA**CACGGTGAAGGTACTTTCACTTCTGATTTGT CTAAGCAAATGG**-3' (SEQ ID NO:850)

EXTC-2: 5'- TCTTCAACCATTCAATGAACAATCTAACAGCTTCTTCTTCCATTTGCTTAGACAA ATCAGAAGT–3' (SEQ ID NO:851)

EXTC-3: 5'- AGATTGTTCATTGAATGGTTGAAGAACGGTGGTCCATCTTCTGGTGCTCCACCA CCATCTGATG-3' (SEQ ID NO:852)

EXTC-4: 5'-AGACTTTAA*ATCGAT*GAGCAACCTCACTCTTGTGTGCATC**AGATGGTGGTGGAG CACCAGAAGA**–3' (SEQ ID NO:853)

EXTC-1 incorporates a SalI cloning site (shown in italics) and the DNA encoding the first 14 amino acids (shown in bold) of the ORF of the mature form of EXENDIN4, i.e. His-48

to Met-61. In EXTC-4, the italicized sequence is a ClaI site; and the ClaI site and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. In EXTC-4, the bolded sequence is the reverse complement of the 24 nucleotides encoding the last 8 amino acid residues Ser-79 to Ser-86 of the mature form of EXENDIN4. Using these two primers along with EXTC-2 and EXTC-3, the mature EXENDIN4 protein was generated by annealing, extension of the annealed primers, digestion with SalI and ClaI, and subcloning into XhoI/ClaI digested pScCHSA. The NotI fragment from this clone was then ligated into the NotI site of pSAC35 to generate construct ID 2470. Construct ID #2470 encodes an albumin fusion protein containing the chimeric leader sequence, the mature form of EXENDIN4, i.e. His-48 to Ser-86, and the mature form of HSA.

Expression and Purification of Construct ID 2470.

Expression in yeast S. cerevisiae.

[1025] Construct 2470 was transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1026] The cell supernatant containing the secreted EXENDIN4-HSA fusion protein expressed from construct ID #2470 in yeast *S. cerevisiae* was purified as described below (also see Example 4). Briefly, the yeast supernatant was equilibrated to pH 7.4 and loaded onto Pharmacia's Blue Sepharose 6 Fast Flow column. The column was washed in 20 mM Tris pH 7.4/ 200 mM NaCl. The EXENDIN4 albumin fusion was eluted via step elution with NaCl from 0.2 M to 2M. Proteins were ~90% pure. N-terminal sequencing should generate the amino-terminus sequence (i.e. HGEGT) of the mature form of EXENDIN4.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2470.

Method

[1027] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the EXENDIN4 albumin fusion protein encoded by construct 2470 was carried

out as described below in Example 28.

Result

[1028] At all concentrations including 1 nM, 10 nM, and 100 nM, the EXENDIN4 albumin fusion encoded by construct 2470 demonstrated glucose uptake activity in 3T3-L1 adipocytes.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2470.

Method

[1029] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the EXENDIN4 albumin fusion protein encoded by construct 2470 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2470 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1030] The activity of the EXENDIN4 albumin fusion protein encoded by construct 2470 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 13: Construct ID 2469, HSA-Exendin4, Generation

[1031] Construct ID 2469, pSAC35:HSA.EXENDIN4.H48-S86, comprises DNA encoding for a EXENDIN4 albumin fusion protein which has the HSA chimeric leader sequence, i.e. the HSA-kex2 signal peptide, followed by the mature form of HSA fused to the amino terminus of the mature form of EXENDIN4, cloned into the *S. cerevisiae* yeast expression vector pSAC35.

Cloning of EXENDIN4 cDNA for construct 2469

[1032] The DNA encoding the mature form of EXENDIN4 was codon optimized so as not to hybridize to the wild-type DNA encoding the mature form of EXENDIN4. The polynucleotide encoding the codon optimized EXENDIN4 was generated with four overlapping primers EXTN-1, EXTN-2, EXTN-3, and EXTN-4, described below, with optimal codon usage for yeast *S. cerevisiae*, that were annealed, extended, cut with Bsu36I/AscI, and ligated into Bsu36I/AscI cut pScNHSA. After sequence confirmation, the NotI fragment encompassing the EXENDIN4 albumin fusion was subcloned into pSAC35. Construct ID #2469 encodes an albumin fusion protein containing the chimeric leader sequence and mature form of HSA and the mature form of EXENDIN4, His-48 to Ser-86.

[1033] Four overlapping oligonucleotides suitable for synthesis of the polynucleotide encoding the mature form of EXENDIN4, EXTN-1, EXTN-2, EXTN-3, and EXTN-4, are:

EXTN-1:5'GTCAAGCTG*CCTTAGGC*TTA**CACGGTGAAGGTACTTTCACTTCTGATTTGTCT AAGCAAA**-3' (SEQ ID NO:854)

EXTN-2:5'-CCATTCAATGAACAATCTAACAGCTTCTTCTTCCATTTGCTTAGACAAATCAGAA GTGAA-3' (SEQ ID NO:855)

EXTN-3:5'-AGCTGTTAGATTGTTCATTGAATGGTTGAAGAACGGTGGTCCATCTTCTGGTGCT CCACC-3' (SEQ ID NO:856)

EXTN-4:5'-ATCGCATAT*GGCGCGCCC*TATTA**AGATGGTGGTGGAGCACCAGAAGATGGAC CACCGTT**-3' (SEQ ID NO:857)

[1034] EXTN-1 incorporates a Bsu36I cloning site (shown in italics) and the DNA encoding the first 13 amino acids (shown in bold) of the ORF of the mature form of EXENDIN4, i.e. His-48 to Gln-60. In EXTN-4, the italicized sequence is an AscI site and the last 36 nucleotides in bold are the reverse complement of DNA encoding the last 12 amino acid residues Asn-75 to Ser-86 of the mature form of EXENDIN4 (for general construct cloning see Example 2). Using these two primers along with EXTN-2 and EXTN-3, the mature EXENDIN4 protein was generated by annealing, extension of the annealed primers, digestion with Bsu36I and AscI, and subcloning into Bsu36I/AscI digested pScNHSA. The NotI fragment from this clone was then ligated into the NotI site of pSAC35 to generate construct ID 2469.

Expression and Purification of Construct ID 2469.

Expression yeast S. cerevisiae.

[1035] Construct 2469 was transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1036] The cell supernatant containing the secreted HSA–EXENDIN4 fusion protein expressed from construct ID #2469 in yeast *S. cerevisiae* was purified as described below (also see Example 4). Specifically, the yeast supernatant was equilibrated to pH 7.4 and loaded directly onto Pharmacia's Blue Sepharose 6 Fast Flow column. The column was washed in 20 mM Tris pH 7.4 + 200 mM NaCl and eluted via step elution with NaCl from 0.2 M to 2 M. Proteins were ~90% pure. N-terminal sequencing should generate the amino-terminus sequence (i.e. DAHKS) of the mature form of HSA.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2469.

Method

[1037] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the EXENDIN4 albumin fusion protein encoded by construct 2469 was carried out as described below in Example 28.

Result

[1038] At all concentrations including 1 nM, 10 nM, and 100 nM, the EXENDIN4 albumin fusion encoded by construct 2469 demonstrated glucose uptake activity in 3T3-L1 adipocytes.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2469.

Method

[1039] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the

EXENDIN4 albumin fusion protein encoded by construct 2469 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2469 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1040] The activity of the EXENDIN4 albumin fusion protein encoded by construct 2469 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: In vivo Mouse Model of NIDDM".

Example 14: Construct ID 2328 and 2359, HLDOU18-HSA, Generation

[1041] Construct ID 2328, pC4.HLDOU18:K23-R429.HSA, encodes for an HLDOU18-HSA fusion protein which comprises the HSA chimeric leader sequence and the mature bone-morphogenic protein 9, "HLDOU18", protein, i.e. K23-R429, fused to the amino-terminus of the mature form of HSA cloned into the mammalian expression vector pC4.

[1042] Construct ID 2359, pEE12.1.HLDOU18:K23-R429.HSA, encodes for an HLDOU18-HSA fusion protein which comprises the HSA chimeric leader sequence and the mature bone-morphogenic protein 9, "HLDOU18", protein, i.e. K23-R429, fused to the amino-terminus of the mature form of HSA cloned into the mammalian expression vector pEE12.1.

Cloning of HLDOU18 cDNA for constructs 2328 and 2359

[1043] The DNA encoding HLDOU18 was amplified with primers HLDOU18-1 and HLDOU18-2, described below, cut with XhoI/ClaI, and ligated into XhoI/ClaI cut pC4:HSA. Construct ID #2328 encodes an albumin fusion protein containing the chimeric leader sequence of HSA and the mature form of HLDOU18, followed by the mature HSA protein.

[1044] Two oligonucleotides suitable for PCR amplification of the polynucleotide

encoding the mature form of HLDOU18, HLDOU18-1 and HLDOU18-2, were synthesized.

HLDOU18-1:5'-CCGCCG*CTCGAG*GGGTGTGTTTCGTCGAAAGCCACTGCAGAGCTGGGGA-3' (SEQ ID NO:286)

HLDOU18-2:5'-AGTCCC*ATCGAT*GAGCAACCTCACTCTTGTGTGCATCCCTGCACCCACACTCTGC-3' (SEQ ID NO:287).

HLDOU18-1 incorporates a XhoI cloning site (shown in italics), DNA encoding for the last seven amino acids of the chimeric leader sequence of HSA, and DNA encoding the first 7 amino acids of the ORF of the mature form of HLDOU18 (shown in bold). In HLDOU18-2, the ClaI site (shown in italics) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. In HLDOU18-2, the bolded sequence is the reverse complement of the last 18 nucleotides encoding amino acid residues Ala-424 to Arg-429 of the mature form of HLDOU18. Using these two primers, the mature form of HLDOU18 protein was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1045] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Xho*I and *Cla*I. After further purification of the *Xho*I-*Cla*I fragment by gel electrophoresis, the product was cloned into *Xho*I/*Cla*I digested pC4:HSA to give construct ID # 2328.

[1046] A HindIII/EcoRI fragment encompassing the HLDOU18 albumin fusion was also subcloned from construct 2328 into the mammalian expression vector pEE12.1 generating construct ID # 2359 to be used in the NS0 expression system.

[1047] The DNA encoding the mature form of HLDOU18 can also be codon optimized so as not to hybridize to the wild-type DNA encoding the mature form of HLDOU18. The polynucleotide encoding the codon optimized HLDOU18 can be generated with overlapping synthetic primers that take advantage of optimal codon usage for mammalian cell-line expression. After PCR amplification and digestion of the codon optimized DNA encoding the mature form of HLDOU18 with the desired restriction enzymes, subsequent construction of appropriate expression vectors comprising the chimeric leader sequence of HSA fused to this codon optimized DNA encoding the mature form of HLDOU18 fused to

the amino-terminus of the mature form of HSA can be carried out as previously described in Example 5 and as described above.

[1048] Further analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected HLDOU18 sequence.

Expression and Purification of Construct ID 2328 and 2359.

Expression in either 293T, CHO or NS0 cells.

[1049] Construct 2328 can be transfected into either 293T cells or CHO cells by methods known in the art (e.g., lipofectamine transfection) and selected with 100 nM methotrexate (see Example 5). Construct 2359 can be transfected into NS0 cells also by methods known in the art.

Purification from 293T cell supernatant.

[1050] The 293T cell supernatant containing the secreted HLDOU18-albumin fusion protein expressed from construct ID #2328 in 293T cells can be purified as described in Example 6.

Purification from CHO cell supernatant.

[1051] The cell supernatant containing the HLDOU18-albumin fusion protein expressed from construct ID #2328 in CHO cells can be purified as described in Example 7.

Purification from NS0 cell supernatant.

[1052] The cell supernatant containing the HLDOU18-albumin fusion protein expressed from construct ID #2359 in NS0 cells can be purified as described in Example 7.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2328 and 2359.

Method

[1053] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the HLDOU18 albumin fusion protein encoded by either construct 2328 or construct 2359 can be carried out as described below in Example 28. Other assays known in the art used to test HLDOU18's involvement in insulin action can also be employed including, but not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase

kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2328 and 2359.

Method

[1054] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the HLDOU18 albumin fusion protein encoded by either constructs 2328 or 2359 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2328 or by construct 2359 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

The activity of the HLDOU18 albumin fusion protein encoded by construct 2328 or by construct 2359 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 15: Construct ID 2340 and 2362, HSA-HLDOU18, Generation

[1055] Construct ID 2340, pC4.HSA.HLDOU18:K23-R429, encodes for an HSA-HLDOU18 fusion protein which comprises the HSA chimeric leader sequence and the mature form of HSA fused to the amino-terminus of the mature bone-morphogenic protein 9, "HLDOU18", protein, i.e. K23-R429, cloned into the mammalian expression vector pC4.

[1056] Construct ID 2362, pEE12.1.HSA.HLDOU18:K23-R429, encodes for an HSA-HLDOU18 fusion protein which comprises the HSA chimeric leader sequence and the

mature form of HSA fused to the amino-terminus of the mature bone-morphogenic protein 9, "HLDOU18", protein, i.e. K23-R429, cloned into the mammalian expression vector pEE12.1.

Cloning of HLDOU18 cDNA for constructs 2340 and 2362

[1057] The DNA encoding the mature form of HLDOU18 was amplified with primers HLDOU18-3 and HLDOU18-4, described below, cut with Bsu36I/Asp718, and ligated into Bsu36I/Asp718 cut pC4:HSA. Construct ID #2340 encodes an albumin fusion protein containing the chimeric leader sequence and the mature form of HSA fused to the amino-terminus of the mature form of HLDOU18 protein.

[1058] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the mature form of HLDOU18, HLDOU18-3 and HLDOU18-4, were synthesized.

HLDOU18-3: 5'- AAGCTG*CCTTAGG*CTTAAAGCCACTGCAGAGCTGG -3' (SEQ ID NO:288)

HLDOU18-4: 5'- GCGCG*GGTACC*TTACTACCTGCACCCACACTCTG -3' (SEQ ID NO:289)

HLDOU18-3 incorporates a Bsu36I cloning site (shown in italics) and encodes the first 6 amino acids (shown in bold) of the ORF of the mature form of HLDOU18. In HLDOU18-4, the italicized sequence is an Asp718 site; the Asp718 site and the DNA following it are the reverse complement of DNA encoding the last 6 amino acids (shown in bold) of the mature HLDOU18 protein. In HLDOU18-4, the bolded sequence is the reverse complement of the last 22 nucleotides encoding amino acid residues Glu-425 to Arg-429 of the mature form of HLDOU18. Using these two primers, the mature HLDOU18 protein was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1059] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bsu36*I and *Asp718*. After further purification of the *Bsu36*I-*Asp718* fragment by gel electrophoresis, the product was cloned into *Bsu36I*/*Asp*718 digested pC4:HSA to give construct ID # 2340.

[1060] A HindIII/EcoRI fragment encompassing the HLDOU18 albumin fusion was also subcloned from construct 2340 into the mammalian expression vector pEE12.1 generating construct ID # 2362 to be used in the NS0 expression system.

[1061] The DNA encoding the mature form of HLDOU18 can also be codon optimized

so as not to hybridize to the wild-type DNA encoding the mature form of HLDOU18. The polynucleotide encoding the codon optimized HLDOU18 can be generated with overlapping synthetic primers that take advantage of optimal codon usage for mammalian cell-line expression. After PCR amplification and digestion of the codon optimized DNA encoding the mature form of HLDOU18 with the desired restriction enzymes, subsequent construction of appropriate expression vectors comprising the chimeric leader sequence of and the mature form of HSA fused to the codon optimized DNA encoding the mature form of HLDOU18 can be carried out as previously described in Example 5 and as described above.

[1062] Further analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected mature HSA sequence.

Expression and Purification of Construct ID 2340 and 2362.

Expression in either 293T, CHO or NS0 cells.

[1063] Construct 2340 can be transfected into either 293T cells or CHO cells by methods known in the art (e.g., lipofectamine transfection) and selected with 100 nM methotrexate (see Example 5). Construct 2362 can be transfected into NS0 cells also by methods known in the art.

Purification from 293T cell supernatant.

[1064] The 293T cell supernatant containing the secreted HLDOU18 albumin fusion protein expressed from construct ID #2340 in 293T cells can be purified as described in Example 6.

Purification from CHO cell supernatant.

[1065] The cell supernatant containing the HLDOU18 albumin fusion protein expressed from construct ID #2340 in CHO cells can be purified as described in Example 6.

Purification from NS0 cell supernatant.

[1066] The cell supernatant containing the HLDOU18 albumin fusion protein expressed from construct ID #2362 in NS0 cells can be purified as described in Example 6.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2340 and 2362.

Method

[1067] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the HLDOU18 albumin fusion protein encoded by either construct 2340 or construct 2362 can be carried out as described below in Example 28. Other assays known in the art used to test HLDOU18 albumin fusions' involvement in insulin action can also be employed including, but not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2340 and 2362.

Method

[1068] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the HLDOU18 albumin fusion protein encoded by either constructs 2340 or 2362 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2340 or by construct 2362 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1069] The activity of the HLDOU18 albumin fusion protein encoded by construct 2340 or by construct 2362 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 16: Construct ID 2369 and 2370, HLDOU18-HSA, Generation

[1070] Construct ID 2369, pC4.HLDOU18:M1-R429.HSA, encodes for an HLDOU18-HSA fusion protein which comprises the full-length of bone-morphogenic protein 9, "HLDOU18", protein, i.e. M1-R429, which includes its native signal sequence, fused to the amino-terminus of the mature form of HSA cloned into the mammalian expression vector pC4.

[1071] Construct ID 2370, pEE12.1.HLDOU18:M1-R429.HSA, encodes for an HLDOU18-HSA fusion protein which comprises the full-length of bone-morphogenic protein 9, "HLDOU18", protein, i.e. M1-R429, which includes its native signal sequence, fused to the amino-terminus of the mature form of HSA cloned into the mammalian expression vector pEE12.1.

Cloning of HLDOU18 cDNA for constructs 2369 and 2370

[1072] The DNA encoding the full-length HLDOU18 was amplified with primers HLDOU18-5 and HLDOU18-6, described below, cut with BamHI/ClaI, and ligated into BamHI/ClaI cut pC4:HSA. Construct ID #2369 encodes an albumin fusion protein containing the full-length form of HLDOU18 which includes its native signal sequence, followed by the mature HSA protein.

[1073] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the full-length form of HLDOU18, HLDOU18-5 and HLDOU18-6, were synthesized.

HLDOU18-5:5'- AATTAA*GGATCC*AAGCTTGCCACCATGTGTCCTGGGGCACTGTGG-3' (SEQ ID NO: 300)

HLDOU18-6:5'-

AGTCCC*ATCGAT*GAGCAACCTCACTCTTGTGTGCATCCCTGCACCCACACTCTGCCACG CTC-3' (SEQ ID NO:301)

HLDOU18-5 incorporates a BamHI cloning site (shown in italics), the Kozak sequence shown underlined, and DNA encoding the first 7 amino acids of the ORF of the full-length form of HLDOU18 (shown in bold), i.e. M-1 to Trp-7. In HLDOU18-6, the ClaI site (shown in italics) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. In HLDOU18-6, the bolded sequence is the reverse complement of the last 25 nucleotides encoding amino acid residues Ser-422

to Arg-429 of the full-length form of HLDOU18. Using these two primers, the full-length form of HLDOU18 protein was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1074] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *BamHI* and *ClaI*. After further purification of the *BamHI-ClaI* fragment by gel electrophoresis, the product was cloned into *BamHI/ClaI* digested pC4:HSA to give construct ID # 2369.

[1075] A HindIII/EcoRI fragment encompassing the HLDOU18 albumin fusion was also subcloned from construct 2369 into the mammalian expression vector pEE12.1 generating construct ID # 2370 to be used in the NS0 expression system.

[1076] The DNA encoding the full-length form of HLDOU18 can also be codon optimized so as not to hybridize to the wild-type DNA encoding the full-length form of HLDOU18. The polynucleotide encoding the codon optimized HLDOU18 can be generated with overlapping synthetic primers that take advantage of optimal codon usage for mammalian cell-line expression. After PCR amplification and digestion of the codon optimized DNA encoding the full-length form of HLDOU18 with the desired restriction enzymes, subsequent construction of appropriate expression vectors comprising the native leader sequence and mature form of HLDOU18 encoded by this codon optimized DNA fused to the amino-terminus of the mature form of HSA can be carried out as previously described in Example 5 and as described above.

[1077] Further analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected HLDOU18 sequence.

Expression and Purification of Construct ID 2369 and 2370.

Expression in either 293T, CHO or NS0 cells.

[1078] Construct 2369 can be transfected into either 293T cells or CHO cells by methods known in the art (e.g., lipofectamine transfection) and selected with 100 nM methotrexate (see Example 5). Construct 2370 can be transfected into NS0 cells also by methods known in the art.

Purification from 293T cell supernatant.

[1079] The 293T cell supernatant containing the secreted HLDOU18 albumin fusion protein expressed from construct ID #2369 in 293T cells can be purified as described in

Example 6.

Purification from CHO cell supernatant.

[1080] The cell supernatant containing the HLDOU18 albumin fusion protein expressed from construct ID #2369 in CHO cells can be purified as described in Example 6.

Purification from NS0 cell supernatant.

[1081] The cell supernatant containing the HLDOU18 albumin fusion protein expressed from construct ID #2370 in NS0 cells can be purified as described in Example 6.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2369 and 2370.

Method

[1082] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the HLDOU18 albumin fusion protein encoded by either construct 2369 or construct 2370 can be carried out as described below in Example 28. Other assays known in the art used to test HLDOU18 albumin fusions' involvement in insulin action can also be employed including, but not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2369 and 2370.

Method

[1083] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the HLDOU18 albumin fusion protein encoded by either construct 2369 or 2370 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2369 or by construct 2370 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1084] The activity of the HLDOU18 albumin fusion protein encoded by construct 2369 or by construct 2370 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: In vivo Mouse Model of NIDDM".

Example 17: Construct ID 2350, HLDOU18 S320-R429-HSA, Generation

[1085] Construct ID 2350, pC4.MPIF.HLDOU18:S320-R429.HSA, encodes for an HLDOU18-HSA fusion protein which comprises the Myeloid Progenitor Inhibitor Factor (MPIF) signal sequence fused to the amino-terminus of a fragment of the bone-morphogenic protein 9, "HLDOU18", protein, i.e. S320-R429, fused to the amino-terminus of the mature form of HSA cloned into the mammalian expression vector pC4.

Cloning of HLDOU18 cDNA for construct 2350.

[1086] The DNA encoding a fragment of HLDOU18, i.e. Ser-320 to Arg-429, fused to the MPIF signal sequence was amplified with primers HLDOU18-7 and HLDOU18-8, described below, cut with BglII/ClaI, and ligated into BglII/ClaI cut pC4:HSA. Construct ID #2350 encodes an albumin fusion protein containing the MPIF signal sequence fused to the amino-terminus of a fragment of HLDOU18, i.e. Ser-320 to Arg-429, followed by the mature HSA protein.

[1087] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding a fragment of HLDOU18, HLDOU18-7 and HLDOU18-8, were synthesized.

HLDOU18-7:5'- GCCGGAA*GATCT*CCGCCACCATGAAGGTCTCCGTGGCTGCCCTCTCCT GCCTCATGCTTGTTACTGCCCTTGGATCCCAGGCCAGCGCCGGGGCTGGCAGCCAC-3' (SEQ ID NO:292)

HLDOU18-8:5'-AGTCCC*ATCGAT*GAGCAACCTCACTCTTGTGTGCATCCCTGCACCCACACT CTGCCACGC-3' (SEQ ID NO:293)

HLDOU18-7 incorporates a BglII cloning site (shown in italics), the DNA encoding the

signal peptide of MPIF, and DNA encoding the 6 amino acid residues Ser-320 to Ser-325 of HLDOU18 (shown in bold). In HLDOU18-8, the ClaI site (shown in italics) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. In HLDOU18-8, the bolded sequence is the reverse complement of the last 23 nucleotides encoding amino acid residues Val-423 to Arg-429 of HLDOU18. Using these two primers, the fragment Ser-320 to Arg-429 of HLDOU18 protein was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1088] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *BglII* and *ClaI*. After further purification of the *BglII-ClaI* fragment by gel electrophoresis, the product was cloned into *BglII/ClaI* digested pC4:HSA to give construct ID # 2350.

[1089] The DNA encoding the Ser-320 to Arg-429 fragment of HLDOU18 can also be codon optimized so as not to hybridize to the wild-type DNA encoding that fragment. The polynucleotide encoding the codon optimized fragment of HLDOU18 can be generated with overlapping synthetic primers that take advantage of optimal codon usage for mammalian cell-line expression. After PCR amplification and digestion of the codon optimized DNA encoding the Ser-320 to Arg-429 fragment of HLDOU18 with the desired restriction enzymes, subsequent construction of appropriate expression vectors comprising the MPIF leader sequence fused to this codon optimized DNA encoding fragment Ser-320 to Arg-429 of HLDOU18 fused to the amino-terminus of the mature form of HSA can be carried out as previously described in Example 5 and as described above.

[1090] Further analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected HLDOU18 sequence.

Expression and Purification of Construct ID 2350.

Expression in either 293T or CHO cells.

[1091] Construct 2350 can be transfected into either 293T cells or CHO cells by methods known in the art (e.g., lipofectamine transfection) and selected with 100 nM methotrexate (see Example 5).

Purification from 293T cell supernatant.

[1092] The 293T cell supernatant containing the secreted HLDOU18 albumin fusion protein expressed from construct ID #2350 in 293T cells can be purified as described in Example 6.

Purification from CHO cell supernatant.

[1093] The cell supernatant containing the HLDOU18 albumin fusion protein expressed from construct ID #2350 in CHO cells can be purified as described in Example 6.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2350.

Method

[1094] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the HLDOU18 albumin fusion protein encoded by construct 2350 can be carried out as described below in Example 28. Other assays known in the art used to test HLDOU18 albumin fusions' involvement in insulin action can also be employed including, but not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2350.

Method

[1095] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the HLDOU18 albumin fusion protein encoded by construct 2350 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2350 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1096] The activity of the HLDOU18 albumin fusion protein encoded by construct 2350 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: In vivo Mouse Model of NIDDM".

Example 18: Construct ID 2351, HSA-HLDOU18 S320-R429, Generation

[1097] Construct ID 2351, pC4.HSA.HLDOU18:S320-R429, encodes for an HSA-HLDOU18 fusion protein which comprises the HSA chimeric leader sequence and the mature form of HSA fused to the amino-terminus of a fragment of the bone-morphogenic protein 9, "HLDOU18", protein, i.e. S320-R429, cloned into the mammalian expression vector pC4.

Cloning of HLDOU18 cDNA for construct 2351.

[1098] The DNA encoding HLDOU18 was amplified with primers HLDOU18-9 and HLDOU18-10, described below, cut with Bsu36I/Asp718, and ligated into Bsu36I/Asp718 cut pC4:HSA. Construct ID #2351 encodes an albumin fusion protein containing the chimeric leader sequence and the mature form of HSA, followed by the S320-R429 fragment of HLDOU18.

[1099] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the HLDOU18 fragment, HLDOU18-9 and HLDOU18-10, were synthesized.
HLDOU18-9: 5'-AAGCTG*CCTTAGG*CTTAAGCGCCGGGGCTGGC-3' (SEQ ID NO:294)
HLDOU18-10: 5'-GCCCGG*GGTACC*CTACCTGCACCCACACTCTGCC-3' (SEQ ID NO:295)
HLDOU18-9 incorporates a Bsu36I cloning site (shown in italics) and encodes the 5 amino acid residues Ser-320 to Gly-324 (shown in bold) of HLDOU18. In HLDOU18-10, the italicized sequence is an Asp718 site; the Asp718 site and the DNA following it are the reverse complement of DNA encoding the last 6 amino acids (shown in bold) of the mature HLDOU18 protein. In HLDOU18-10, the bolded sequence is the reverse complement of the last 22 nucleotides encoding amino acid residues Ala-424 to Arg-429

of the mature form of HLDOU18. Using these two primers, the Ser-320 to Arg-429 fragment of the HLDOU18 protein was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1100] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bsu36*I and *Asp718*. After further purification of the *Bsu36*I-*Asp718* fragment by gel electrophoresis, the product was cloned into *Bsu36*I/*Asp*718 digested pC4:HSA to give construct ID # 2351.

[1101] A HindIII/EcoRI fragment encompassing the HLDOU18 albumin fusion can also be subcloned from construct 2351 into the mammalian expression vector pEE12.1 to be used in the NS0 expression system.

[1102] The DNA encoding the Ser-320 to Arg-429 fragment of HLDOU18 can also be codon optimized so as not to hybridize to the wild-type DNA encoding that fragment. The polynucleotide encoding the codon optimized fragment of HLDOU18 can be generated with overlapping synthetic primers that take advantage of optimal codon usage for mammalian cell-line expression. After PCR amplification and digestion of the codon optimized DNA encoding the Ser-320 to Arg-429 fragment of HLDOU18 with the desired restriction enzymes, subsequent construction of appropriate expression vectors comprising the chimeric leader sequence and mature form of HSA fused to this codon optimized DNA encoding fragment Ser-320 to Arg-429 of HLDOU18 can be carried out as previously described in Example 5 and as described above.

[1103] Further analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected mature HSA sequence.

Expression and Purification of Construct ID 2351.

Expression in either 293T or CHO cells.

[1104] Construct 2351 can be transfected into either 293T cells or CHO cells by methods known in the art (e.g., lipofectamine transfection) and selected with 100 nM methotrexate (see Example 5).

Purification from 293T cell supernatant.

[1105] The 293T cell supernatant containing the secreted HLDOU18 albumin fusion

protein expressed from construct ID #2351 in 293T cells can be purified as described in Example 6.

Purification from CHO cell supernatant.

[1106] The cell supernatant containing the HLDOU18 albumin fusion protein expressed from construct ID #2351 in CHO cells can be purified as described in Example 6.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2351.

Method

[1107] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the HLDOU18 albumin fusion protein encoded by construct 2351 can be carried out as described below in Example 28. Other assays known in the art used to test HLDOU18 albumin fusions' involvement in insulin action can also be employed including, but not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2351.

Method

[1108] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the HLDOU18 albumin fusion protein encoded by either constructs 2351 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2351 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1109] The activity of the HLDOU18 albumin fusion protein encoded by construct 2351 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 19: Construct ID 2053, IFNb-HSA, Generation

[1110] Construct ID 2053, pEE12.1:IFNb.HSA, comprises DNA encoding an IFNb albumin fusion protein which has the full-length IFNb protein including the native IFNb leader sequence fused to the amino-terminus of the mature form of HSA in the NS0 expression vector pEE12.1.

Cloning of IFNb cDNA

[1111] The polynucleotide encoding IFNb was PCR amplified using primers IFNb-1 and IFNb-2, described below, cut with *Bam* HI/*Cla* I, and ligated into *Bam* HI/*Cla* I cut pC4:HSA, resulting in construct 2011. The *Eco* RI/*Eco* RI fragment from Construct ID # 2011 was subcloned into the *Eco* RI site of pEE12.1 generating construct ID #2053 which which comprises DNA encoding an albumin fusion protein containing the leader sequence and the mature form of IFNb, followed by the mature HSA protein.

[1112] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the full-length of IFNb, IFNb-1 and IFNb-2, were synthesized:

IFNb-1: 5'- GCGCGGATCCGAATT*CCGCCGCCATG*ACCAACAAGTGTCTCCTCCA AATTGCTCTCCTGTTGTGCTTCTCCACTACAGCTCTTTCCATGAGCTACAACTT GCTTGG-3' (SEQ ID NO:256)

IFNb-2: 5'- GCGCGCATCGATGAGCAACCTCACTCTTGTGTGCATCGTTTCGGA GGTAACCTGT-3' (SEQ ID NO:257)

[1113] The IFNb-1 primer incorporates a *Bam* HI cloning site (shown underlined), an *Eco* RI cloning site, and a Kozak sequence (shown in italics), followed by 80 nucleotides encoding the first 27 amino acids of the full-length form of IFNb. In IFNb-2, the *Cla* I site (shown underlined) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein (SEQ ID NO:327) and the

last 18 nucleotides are the reverse complement of DNA encoding the last 6 amino acid residues of IFNb (see Example 2). A PCR amplimer was generated using these primers, purified, digested with *Bam* HI and *Cla* I restriction enzymes, and cloned into the *Bam* HI and *Cla* I sites of the pC4:HSA vector. After the sequence was confirmed, an *Eco* RI fragment containing the IFNb albumin fusion protein expression cassette was subcloned into *Eco* RI digested pEE12.1.

[1114] Further, analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing can confirm the presence of the expected IFNb sequence (see below).

[1115] IFNb albumin fusion proteins of the invention preferably comprise the mature form of HSA , i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the mature form of IFNb, i.e., Met-22 to Asn-187. In one embodiment of the invention, IFNb albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature IFNb albumin fusion protein is secreted directly into the culture medium. IFNb albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, IFNb albumin fusion proteins of the invention comprise the native IFNb. In further preferred embodiments, the IFNb albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2053.

Expression in murine myeloma NS0 cell-lines.

[1116] Construct ID # 2053, pEE12.1:IFNb-HSA , was electroporated into NS0 cells by methods known in the art (see Example 6).

Purification from NS0 cell supernatant.

[1117] Purification of IFNb-HSA from NS0 cell supernatant may follow the methods described in Example 7 which involve Q-Sepharose anion exchange chromatography at pH 7.4 using a NaCl gradient from 0 to 1 M in 20 mM Tris-HCl, followed by Poros PI 50 anion exchange chromatography at pH 6.5 with a sodium citrate gradient from 5 to 40 mM, and diafiltrating for 6 DV into 10 mM citrate, pH 6.5 and 140 mM NaCl, the final buffer composition. N-terminal sequencing should yield the sequence MSYNLL which is the amino terminus of the mature form of IFNb. The protein has an approximate MW of 88.5 kDa.

[1118] For larger scale purification, e.g., 50 L of NS0 cell supernatant can be concentrated into ~8 to 10 L. The concentrated sample can then be passed over the Q-Sepharose anion exchange column (10 x 19 cm, 1.5 L) at pH 7.5 using a step elution consisting of 50 mM NaOAc, pH 6.0 and 150 mM NaCl. The eluted sample can then be virally inactivated with 0.75% Triton-X 100 for 60 min at room temperature. SDR-Reverse Phase chromatography (10 cm x 10 cm, 0.8 L) can then be employed at pH 6.0 with 50 mM NaOAc and 150 mM NaCl, or alternatively, the sample can be passed over an SP-sepharose column at pH 4.8 using a step elution of 50 mM NaOAc, pH 6.0, and 150 mM NaCl. DV 50 filtration would follow to remove any viral content. Phenyl-650M chromatography (20 cm x 12 cm, 3.8 L) at pH 6.0 using a step elution consisting of 350 mM $(NH_4)_2SO_4$ and 50 mM NaOAc, or alternatively consisting of 50 mM NaOAc pH 6.0, can follow. Diafiltration for 6-8 DV will allow for buffer exchange into the desired final formulation buffer of either 10 mM Na_2HPO_4 + 58 mM sucrose + 120 mM NaCl, pH 7.2 or 10 mM citrate, pH 6.5, and 140 mM NaCl or 25 mM Na_2HPO_4, 100 mM NaCl, pH 7.2.

The activity of IFNb can be assayed using an in vitro ISRE-SEAP assay.

[1119] All type I Interferon proteins signal through a common receptor complex and a similar Jak/STAT signaling pathway that culminates in the activation of Interferon, "IFN", responsive genes through the Interferon Sequence Responsive Element, "ISRE". A convenient assay for type I IFN activity is a promoter-reporter based assay system that contains multiple copies of the ISRE element fused to a downstream reporter gene. A stable HEK293 cell-line can be generated and contains a stably integrated copy of an ISRE-SEAP reporter gene that is extremely sensitive to type I IFNs and displays linearity

over 5 logs of concentration.

Method of Screening of IFNb-HSA NS0 stable clones.

[1120] Construct 2053 was electroporated into NS0 cells as described in Example 6. The NS0 cells transfected with construct ID # 2053 were screened for activity by testing conditioned growth media in the ISRE-SEAP assay. The ISRE-SEAP/293F reporter cells were plated at 3 x 10^4 cell/well in 96-well, poly-D-lysine coated, plates, one day prior to treatment. Reporter cells were treated with various dilutions (including but not limited to 1:500 and 1:5000) of conditioned supernatant or purified preparations of IFNb albumin fusion protein encoded by construct ID 2053 or rhIFNb as a control. The reporter cells were then incubated for 24 hours prior to removing 40 □L for use in the SEAP Reporter Gene Chemiluminescent Assay (Roche catalog # 1779842). Recombinant human Interferon beta, "rhIFNb" (Biogen), was used as a positive control.

Result

[1121] The purified preparation of NS0 expressed IFNb-HSA had a greater EC50 of 9.3 x 10^{-9} g/mL than rhIFNb (Biogen) which had an EC50 of 1.8 x 10^{-10} g/mL (see Figure 6).

In vivo induction of OAS by an Interferon.

Method

[1122] The OAS enzyme, 2'-5'- OligoAdenylate Synthetase, is activated at the transcriptional level by interferon in response to antiviral infection. The effect of interferon constructs can be measured by obtaining blood samples from treated monkeys and analyzing these samples for transcriptional activation of two OAS mRNA, p41 and p69. A volume of 0.5 mL of whole blood can be obtained from 4 animals per group at 7 different time points, day 0, day 1, day 2, day 4, day 8, day 10, and day 14 per animal. The various groups may include injection of vehicle control, intravenous and/or subcutaneous injection of either 30 μg/kg and/or 300 μg/kg IFN albumin fusion protein on day 1, and subcutaneous injection of 40 μg/kg of Interferon alpha (Schering-Plough) as a positive control on days 1, 3, and 5. The levels of the p41 and the p69 mRNA transcripts can be determined by real-time quantitative PCR (Taqman) using probes specific for p41-OAS and p69-OAS. OAS mRNA levels can be quantitated relative to 18S ribosomal RNA

endogenous control.

In vivo induction of OAS by Interferon beta albumin fusion encoded by construct ID 2053.

Method

[1123] The activity of the HSA-IFNb fusion protein encoded by construct 2053 can be assayed in the *in vivo* OAS assay as previously described above under subsection heading, "*In vivo* induction of OAS by an Interferon".

Example 20: Indications for IFNb albumin fusion proteins

[1124] IFN beta albumin fusion proteins (including, but not limited to, those encoded by construct 2053) can be used to treat, prevent, ameliorate and/or detect multiple sclerosis. Other indications include, but are not limited to, melanoma, solid tumors, cancer, bacterial infections, chemoprotection, thrombocytopenia, HIV infections, prostate cancer, cancer, hematological malignancies, hematological disorders, preleukemia, glioma, hepatitis B, hepatitis C, human papillomavirus, pulmonary fibrosis, age-related macular degeneration, brain cancer, glioblastoma multiforme, liver cancer, malignant melanoma, colorectal cancer, Crohn's disease, neurological disorders, non-small cell lung cancer, rheumatoid arthritis, and ulcerative colitis.

Example 21: Construct ID 2250, HSA-Insulin (GYG), Generation

[1125] Construct ID 2250, pSAC35.HSA.INSULIN(GYG).F1-N62, encodes for an HSA-INSULIN (GYG) fusion protein which comprises the HSA chimeric leader sequence and the mature form of HSA fused to the amino-terminus of the synthetic single-chain long-acting insulin analog (INSULIN ($GY^{32}G$)) with a Tyr at position 32, cloned into the yeast *S. cerevisiae* expression vector pSAC35.

Cloning of INSULIN (GYG) cDNA for construct 2250.

[1126] The DNA encoding the synthetic single-chain form of INSULIN (GYG) was PCR generated using four overlapping primers. The sequence corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the C-domain of Insulin Growth Factor 1, "IGF-1" (GY^{32}GSSSRRAPQT) (SEQ ID NO:832), to avoid the

need for proinsulin processing and to ensure proper folding of the single-chain protein. The sequence was codon optimized for expression in yeast *S. cerevisiae*. The PCR fragment was digested and subcloned into *Bsu* 361/*Asc* I digested pScNHSA. A *Not* I fragment was then subcloned into the pSAC35 plasmid. Construct ID #2250 encodes for the chimeric leader sequence and the mature form of HSA fused to the amino-terminus of the synthetic single-chain form of INSULIN (GYG).

[1127] The 5' and 3' primers of the four overlapping oligonucleotides suitable for PCR amplification of the polynucleotide encoding the synthetic single-chain form of INSULIN (GYG), INSULIN (GYG)-1 and INSULIN (GYG)-2, were synthesized:

INSULIN (GYG)-1: 5'-GTCAAGCTG*CCTTAGG*CTTA**TTCGTTAACCAACACTTGTGTGGTT CTCACTTGGTTGAAGCTTTGTACTTGGTTTGTGGTGAA**-3' (SEQ ID NO:268)

INSULIN (GYG)-2: 5'-ATCGCATAT*GGCGCGCC*CTA**TTAGTTACAGTAGTTTTCCAATTG GTACAAAGAACAAATAGAAGTACAA** –3' (SEQ ID NO:269)

INSULIN (GYG)-1 incorporates a *Bsu* 36I cloning site (shown in italics) and encodes the first 21 amino acids (shown in bold) of the ORF of the synthetic single-chain form of INSULIN (GYG). In INSULIN (GYG)-2, the italicized sequence is an *Asc* I site. In INSULIN (GYG)-2, the bolded sequence is the reverse complement of the last 49 nucleotides encoding amino acid residues Cys-49 to Asn-63 of the synthetic single-chain form of INSULIN (GYG). With these two primers, the synthetic single-chain form of INSULIN (GYG) was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1128] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bsu36*I and *AscI*. After further purification of the *Bsu36*I-*AscI* fragment by gel electrophoresis, the product was cloned into *Bsu36I*/*AscI* digested pScNHSA. A *Not* I fragment was further subcloned into pSAC35 to give construct ID # 2250.

[1129] Further analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected mature HSA sequence (see below).

[1130] INSULIN albumin fusion proteins of the invention preferably comprise the mature form of HSA, i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the synthetic single-chain analog of INSULIN, i.e., Phe-1 to Asn–62; the sequence

corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the C-domain of Insulin Growth Factor 1, "IGF-1" (GY^{32}GSSSRRAPQT) (SEQ ID NO:832). In one embodiment of the invention, INSULIN albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature INSULIN albumin fusion protein is secreted directly into the culture medium. INSULIN albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, INSULIN albumin fusion proteins of the invention comprise the native INSULIN. In further preferred embodiments, the INSULIN albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2250.

Expression in yeast S. cerevisiae.

[1131] Construct 2250 can be transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1132] The cell supernatant containing the secreted INSULIN (GYG) albumin fusion protein expressed from construct ID #2250 in yeast *S. cerevisiae* can be purified as described in Example 4. N-terminal sequencing of the albumin fusion protein should result in the sequence DAHKS which corresponds to the amino terminus of the mature form of HSA.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2250.

Method

[1133] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the INSULIN (GYG) albumin fusion protein encoded by construct 2250 was carried out as described below in Example 28. Other assays known in the art that may be used to test INSULIN (GYG) albumin fusion proteins' include, but are not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, and PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

Result

[1134] The supernatant derived from transformed yeast *S. cerevisiae* expressing insulin albumin fusion encoded by construct 2250 demonstrated glucose uptake/transport activity in 3T3-L1 adipocytes (see Figure 2).

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2250.

Method

[1135] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the INSULIN (GYG) albumin fusion protein encoded by construct 2250 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2250 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1136] The activity of the INSULIN (GYG) albumin fusion protein encoded by construct 2250 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 22: Construct ID 2255, Insulin (GYG)-HSA, Generation

[1137] Construct ID 2255, pSAC35.INSULIN(GYG).F1-N62.HSA, encodes for an INSULIN (GYG)-HSA fusion protein which comprises the HSA chimeric leader sequence of HSA fused to the amino-terminus of the synthetic single-chain long-acting insulin analog (INSULIN ($GY^{32}G$)) with a Tyr in position 32, which is, in turn, fused to the mature form of HSA, cloned into the yeast *S. cerevisiae* expression vector pSAC35.

Cloning of INSULIN (GYG) cDNA for construct 2255.

[1138] The DNA encoding the synthetic single-chain form of INSULIN (GYG) was PCR generated using four overlapping primers. The sequence corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the C-domain of Insulin Growth Factor 1, "IGF-1" (GY^{32}GSSSRRAPQT) (SEQ ID NO: 832), to avoid the need for proinsulin processing and to ensure proper folding of the single-chain protein. The sequence was codon optimized for expression in yeast *S. cerevisiae*. The PCR fragment was digested with *Sal I/Cla* I and subcloned into *Xho I/Cla* I digested pScCHSA. A *Not* I fragment was then subcloned into the pSAC35 plasmid. Construct ID #2255 encodes for the chimeric leader sequence of HSA fused to the amino-terminus of the synthetic single-chain form of INSULIN (GYG) followed by the mature form of HSA.

[1139] The 5' and 3' primers of the four overlapping oligonucleotides suitable for PCR amplification of the polynucleotide encoding the synthetic single-chain form of INSULIN (GYG), INSULIN (GYG)-3 and INSULIN (GYG)-4, were synthesized:

INSULIN (GYG)-3: 5'-TCCAGGAGC*GTCGAC*AAAAGATTCGTTAACCAACACTTGTGTGG TTCTCACTTGGTTGAAGCTTTGTACTTGGTTTGTGGTGAA -3' (SEQ ID NO:271)

INSULIN (GYG)-4: 5'-AGACTTTAA*ATCGAT*GAGCAACCTCACTCTTGTGTGCATCGTTAC AGTAGTTTTCCAATTGGTACAAAGAACAAATAGAAGTACAA-3' (SEQ ID NO:272)

INSULIN (GYG)-3 incorporates a *Sal* I cloning site (shown in italics) and the DNA encoding the first 21 amino acids (shown in bold) of the ORF of the synthetic single-chain form of INSULIN(GYG). In INSULIN (GYG)-4, the italicized sequence is a *Cla* I site; and the *Cla* I site and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. The bolded sequence is the reverse complement of the 46 nucleotides encoding the last 15 amino acid residues Cys-49 to Asn-

63 of the synthetic single-chain form of INSULIN (GYG). With these two primers, the synthetic single-chain INSULIN (GYG) protein was generated by annealing, extension of the annealed primers, digestion with *Sal* I and *Cla* I, and subcloning into *Xho I/Cla* I digested pScCHSA. The *Not* I fragment from this clone was then ligated into the *Not* I site of pSAC35 to generate construct ID 2255. Construct ID #2255 encodes an albumin fusion protein containing the chimeric leader sequence, the synthetic single-chain form of INSULIN (GYG), and the mature form of HSA.

[1140] Further analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected INSULIN (GYG) sequence (see below).

[1141] INSULIN albumin fusion proteins of the invention preferably comprise the mature form of HSA, i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the synthetic single-chain analog of INSULIN, i.e., Phe-1 to Asn–62; the sequence corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the C-domain of Insulin Growth Factor 1, "IGF-1" (GY^{32}GSSSRRAPQT) (SEQ ID NO:832). In one embodiment of the invention, INSULIN albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature INSULIN albumin fusion protein is secreted directly into the culture medium. INSULIN albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, INSULIN albumin fusion proteins of the invention comprise the native INSULIN. In further preferred embodiments, the INSULIN albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2255.

Expression in yeast S. cerevisiae.

[1142] Construct 2255 can be transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1143] The cell supernatant containing the secreted INSULIN (GYG) albumin fusion protein expressed from construct ID #2255 in yeast *S. cerevisiae* can be purified as described in Example 4. N-terminal sequencing of the expressed and purified albumin fusion protein should generate FVNQH which corresponds to the amino terminus of the synthetic single-chain long-acting insulin analog (INSULIN ($GY^{32}G$)).

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2255.

Method

[1144] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the INSULIN (GYG) albumin fusion protein encoded by construct 2255 can be carried out as described below in Example 28. Other assays known in the art that may be used to test INSULIN (GYG) albumin fusion proteins' include, but are not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, and PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2255.

Method

[1145] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the INSULIN (GYG) albumin fusion protein encoded by construct 2255 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2255 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1146] The activity of the INSULIN (GYG) albumin fusion protein encoded by construct 2255 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 23: Construct ID 2276, HSA-Insulin (GGG), Generation

[1147] Construct ID 2276, pSAC35.HSA.INSULIN(GGG).F1-N58, encodes for an HSA-INSULIN (GGG) fusion protein which comprises the HSA chimeric leader sequence and the mature form of HSA fused to the amino-terminus of the synthetic single-chain long-acting insulin analog (INSULIN ($GG^{32}G$)) with a Gly at position 32, cloned into the yeast *S. cerevisiae* expression vector pSAC35.

Cloning of INSULIN (GGG) cDNA for construct 2276.

[1148] The DNA encoding the synthetic single-chain form of INSULIN (GGG) was PCR generated using four overlapping primers. The sequence corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the synthetic linker "$GG^{32}GPGKR$" (SEQ ID NO:858) to avoid the need for proinsulin processing and to ensure proper folding of the single-chain protein. The sequence was codon optimized for expression in yeast *S. cerevisiae*. The PCR fragment was digested and subcloned into *Bsu* 361/*Asc* I digested pScNHSA. A *Not* I fragment was then subcloned into the pSAC35 plasmid. Construct ID #2276 encodes for the chimeric leader sequence and the mature form of HSA fused to the amino-terminus of the synthetic single-chain form of INSULIN (GGG).

[1149] The 5' and 3' primers of the four overlapping oligonucleotides suitable for PCR amplification of the polynucleotide encoding the synthetic single-chain form of INSULIN (GGG), INSULIN (GGG)-1 and INSULIN (GGG)-2, were synthesized:

INSULIN (GGG)-5: 5'-GTCAAGCTG*CCTTAGG*CTTATTCGTTAACCAACACTTGTGTGGTT CTCACTTGGTTGAAGCTTTGTACTTGGTTTGTGGTGAA-3' (SEQ ID NO:268)

INSULIN (GGG)-6: 5'-ATCGCATAT*GGCGCGCC*CTATTAGTTACAGTAGTTTTCCAATTG GTACAAAGAACAAATAGAAGTACAA –3' (SEQ ID NO:269)

INSULIN (GGG)-5 incorporates a *Bsu* 36I cloning site (shown in italics) and encodes the first 21 amino acids (shown in bold) of the ORF of the synthetic single-chain form of INSULIN (GGG). In INSULIN (GGG)-6, the italicized sequence is an *Asc* I site. In INSULIN (GGG)-6, the bolded sequence is the reverse complement of the last 49 nucleotides encoding amino acid residues Cys-44 to Asn-58 of the synthetic single-chain form of INSULIN (GGG). With these two primers, the synthetic single-chain form of INSULIN (GGG) was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

[1150] The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bsu36*I and *AscI*. After further purification of the *Bsu36*I-*AscI* fragment by gel electrophoresis, the product was cloned into *Bsu36*I/*AscI* digested pScNHSA. A *Not* I fragment was further subcloned into pSAC35 to give construct ID # 2276.

[1151] Further, analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected mature HSA sequence (see below).

[1152] INSULIN albumin fusion proteins of the invention preferably comprise the mature form of HSA , i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the synthetic single-chain analog of INSULIN, i.e., Phe-1 to Asn–58; the sequence corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the synthetic linker "GG^{32}GPGKR" (SEQ ID NO:858). In one embodiment of the invention, INSULIN albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature INSULIN albumin fusion protein is secreted directly into the culture medium. INSULIN albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred

embodiment, INSULIN albumin fusion proteins of the invention comprise the native INSULIN. In further preferred embodiments, the INSULIN albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2276.

Expression in yeast S. cerevisiae.

[1153] Construct 2276 can be transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1154] The cell supernatant containing the secreted INSULIN (GGG) albumin fusion protein expressed from construct ID #2276 in yeast *S. cerevisiae* can be purified as described in Example 4. N-terminal sequencing should yield DAHKS which corresponds to the amino terminus of the mature form of HSA.

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2276.

Method

[1155] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the INSULIN (GGG) albumin fusion protein encoded by construct 2276 was carried out as described below in Example 28. Other assays known in the art that may be used to test INSULIN (GGG) albumin fusion proteins' include, but are not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, and PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

Result

[1156] The supernatant derived from transformed yeast *S. cerevisiae* expressing insulin albumin fusion encoded by construct 2276 demonstrated glucose uptake/transport activity in 3T3-L1 adipocytes (see Figure 2).

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2276.

Method

[1157] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the INSULIN (GGG) albumin fusion protein encoded by construct 2276 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2276 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1158] The activity of the INSULIN (GGG) albumin fusion protein encoded by construct 2276 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 24: Construct ID 2278, Insulin (GGG)-HSA, Generation

[1159] Construct ID 2278, pSAC35.INSULIN(GGG).HSA, encodes for an INSULIN (GGG)-HSA fusion protein which comprises the HSA chimeric leader sequence of HSA fused to the amino-terminus of the synthetic single-chain long-acting insulin analog (INSULIN (GG^{32}G)) with a Gly in position 32, which is, in turn, fused to the mature form of HSA, cloned into the yeast *S. cerevisiae* expression vector pSAC35.

Cloning of INSULIN (GGG) cDNA for construct 2278.

[1160] The DNA encoding the synthetic single-chain form of INSULIN (GGG) was PCR generated using four overlapping primers. The sequence corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the synthetic linker "GG^{32}GPGKR" (SEQ ID NO:858) to avoid the need for proinsulin processing and to

ensure proper folding of the single-chain protein. The sequence was codon optimized for expression in yeast *S. cerevisiae*. The PCR fragment was digested with *Sal I/Cla* I and subcloned into *Xho I/Cla* I digested pScCHSA. A *Not* I fragment was then subcloned into the pSAC35 plasmid. Construct ID #2278 encodes for the chimeric leader sequence of HSA fused to the amino-terminus of the synthetic single-chain form of INSULIN (GGG) followed by the mature form of HSA.

[1161] The 5' and 3' primers of the four overlapping oligonucleotides suitable for PCR amplification of the polynucleotide encoding the synthetic single-chain form of INSULIN (GGG), INSULIN (GGG)-7 and INSULIN (GGG)-8, were synthesized:

INSULIN (GGG)-7: 5'-TCCAGGAGC*GTCGAC*AAAAGA**TTCGTTAACCAACACTTGTGTGG TTCTCACTTGGTTGAAGCTTTGTACTTGGTTTGTGGTGAA** -3' (SEQ ID NO:275)

INSULIN (GGG)-8: 5'-AGACTTTAA*ATCGAT*GAGCAACCTCACTCTTGTGTGCATCG**TTAC AGTAGTTTTCCAATTGGTACAAAGAACAAATAGAAGTACAA**–3' (SEQ ID NO:276)

INSULIN (GGG)-7 incorporates a *Sal* I cloning site (shown in italics) and the DNA encoding the first 21 amino acids (shown in bold) of the ORF of the synthetic single-chain form of INSULIN(GGG). In INSULIN (GGG)-8, the italicized sequence is a *Cla* I site; and the *Cla* I site and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein. The bolded sequence is the reverse complement of the 46 nucleotides encoding the last 15 amino acid residues Cys-44 to Asn-58 of the synthetic single-chain form of INSULIN (GGG). With these two primers, the synthetic single-chain INSULIN (GGG) protein was generated by annealing, extension of the annealed primers, digestion with *Sal* I and *Cla* I, and subcloning into *Xho I/Cla* I digested pScCHSA. The *Not* I fragment from this clone was then ligated into the *Not* I site of pSAC35 to generate construct ID 2278. Construct ID #2278 encodes an albumin fusion protein containing the chimeric leader sequence, the synthetic single-chain form of INSULIN (GGG), and the mature form of HSA.

[1162] Further, analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing should confirm the presence of the expected INSULIN (GGG) sequence (see below).

[1163] INSULIN albumin fusion proteins of the invention preferably comprise the mature form of HSA , i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the synthetic single-chain analog of INSULIN, i.e., Phe-1 to Asn–58; the sequence

corresponding to the C-peptide in the middle region of the proinsulin cDNA was replaced by the synthetic linker "GG^{32}GPGKR" (SEQ ID NO:858). In one embodiment of the invention, INSULIN albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature INSULIN albumin fusion protein is secreted directly into the culture medium. INSULIN albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, INSULIN albumin fusion proteins of the invention comprise the native INSULIN. In further preferred embodiments, the INSULIN albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2278.

Expression in yeast S. cerevisiae.

[1164] Construct 2278 can be transformed into yeast *S. cerevisiae* by methods known in the art (see Example 3). Expression levels can be examined by immunoblot detection with anti-HSA serum as the primary antibody.

Purification from yeast S. cerevisiae cell supernatant.

[1165] The cell supernatant containing the secreted INSULIN (GGG) albumin fusion protein expressed from construct ID #2278 in yeast *S. cerevisiae* can be purified as described in Example 4. N-terminal sequencing of the expressed and purified albumin fusion protein should generate FVNQH which corresponds to the amino terminus of the synthetic single-chain long-acting insulin analog (INSULIN (GG^{32}G)).

In vitro [^{3}H]-2-Deoxyglucose Uptake Assay in the presence of the albumin fusion protein encoded by construct 2278.

Method

[1166] The *in vitro* assay to measure the glucose uptake in 3T3-L1 adipocytes in the presence of the INSULIN (GGG) albumin fusion protein encoded by construct 2278 can be carried out as described below in Example 28. Other assays known in the art that may be used to test INSULIN (GGG) albumin fusion proteins' include, but are not limited to, L6 Rat Myoblast Proliferation Assay via glycogen synthase kinase-3 (GSK-3) and H4IIe reporter assays (see Example 35) including the rat Malic Enzyme Promoter (rMEP)-SEAP, Sterol Regulatory Element Binding Protein (SREBP)-SEAP, Fatty Acid Synthetase (FAS)-SEAP, and PhosphoEnolPyruvate CarboxyKinase (PEPCK)-SEAP reporters.

In vitro Pancreatic Cell-lines Proliferation Assay in the presence of the albumin fusion protein encoded by construct 2278.

Method

[1167] The *in vitro* assay to measure the differentiation and proliferation of ductal epithelium pancreatic ARIP cell-line into insulin-producing beta cells and/or to measure the proliferation of the insulin-producing RIN-M beta cell-line in the presence of the INSULIN (GGG) albumin fusion protein encoded by construct 2278 can be carried out as described below under heading: "Example 29: *In vitro* Assay of [^{3}H]-Thymidine Incorporation into Pancreatic Cell-lines".

The activity of the albumin fusion protein encoded by construct 2278 can be assayed in vivo using diabetic NOD and/or NIDDM mouse models.

[1168] The activity of the INSULIN (GGG) albumin fusion protein encoded by construct 2278 can be measured using NOD and/or NIDDM mouse models described below under the headings, "Example 31: Occurrence of Diabetes in NOD Mice", "Example 32: Histological Examination of NOD Mice", and "Example 34: *In vivo* Mouse Model of NIDDM".

Example 25: Indications For Insulin Albumin Fusion Proteins

[1169] Results from *in vitro* assays described above indicate that insulin albumin fusion proteins are useful for the treatment, prevention, and/or diagnosis of hyperglycemia, insulin resistance, insulin deficiency, hyperlipidemia, hyperketonemia, and diabetes

mellitus, Type 1 and Type 2 diabetes.

Example 26: Isolation Of A Selected cDNA Clone From The Deposited Sample

[1170] Many of the albumin fusion constructs of the invention have been deposited with the ATCC as shown in Table 3. The albumin fusion constructs may comprise any one of the following expression vectors, the yeast *S. cerevisiae* expression vector pSAC35, the mammalian expression vector pC4, or the mammalian expression vector pEE12.1.

[1171] pSAC35 (Sleep *et al.*, Biotechnology 8:42 (1990)), pC4 (ATCC Accession No. 209646; Cullen *et al.*, Molecular and Cellular Biology, 438-447 (1985); Boshart *et al.*, Cell 41: 521-530 (1985)), and pEE12.1 (Lonza Biologics, Inc.; Stephens and Cockett, Nucl. Acids Res. 17: 7110 (1989); International Publication #WO89/01036; Murphy *et al.*, Biochem J. 227: 277-279 (1991); Bebbington *et al.*, Bio/Technology 10:169-175 (1992); US patent US 5,122,464; International Publication #WO86/05807) vectors comprise an ampicillin resistance gene for growth in bacterial cells. These vectors and/or an albumin fusion construct comprising them can be transformed into an *E. coli* strain such as Stratagene XL-1 Blue (Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037) using techniques described in the art such as Hanahan, spread onto Luria-Broth agar plates containing 100 µg/mL ampicillin, and grown overnight at 37 °C.

[1172] The deposited material in the sample assigned the ATCC Deposit Number cited in Table 3 for any given albumin fusion construct also may contain one or more additional albumin fusion constructs, each encoding different albumin fusion proteins. Thus, deposits sharing the same ATCC Deposit Number contain at least an albumin fusion construct identified in the corresponding row of Table 3.

[1173] Two approaches can be used to isolate a particular albumin fusion construct from the deposited sample of plasmid DNAs cited for that albumin fusion construct in Table 3.

Method 1: Screening

[1174] First, an albumin fusion construct may be directly isolated by screening the sample of deposited plasmid DNAs using a polynucleotide probe corresponding to SEQ ID NO:X using methods known in the art. For example, a specific polynucleotide with 30-40 nucleotides may be synthesized using an Applied Biosystems DNA synthesizer

according to the sequence reported. The oligonucleotide can be labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982)). The albumin fusion construct from a given ATCC deposit is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Method 2: PCR

[1175] Alternatively, DNA encoding a given albumin fusion protein may be amplified from a sample of a deposited albumin fusion construct with SEQ ID NO:X, for example, by using two primers of 17-20 nucleotides that hybridize to the deposited albumin fusion construct 5' and 3' to the DNA encoding a given albumin fusion protein. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[1176] Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are known in the art. For

instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)).

[1177] Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

[1178] This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

[1179] This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 27: Expression Of An Albumin Fusion Protein In Mammalian Cells

[1180] The albumin fusion proteins of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is

achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[1181] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as, pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, but are not limited to, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[1182] Alternatively, the albumin fusion protein can be expressed in stable cell lines containing the polynucleotide encoding the albumin fusion protein integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

[1183] The transfected polynucleotide encoding the fusion protein can also be amplified to express large amounts of the encoded fusion protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin et al., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page et al., Biotechnology 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

[1184] Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the

gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

[1185] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

[1186] A polynucleotide encoding an albumin fusion protein of the present invention is generated using techniques known in the art and this polynucleotide is amplified using PCR technology known in the art. If a naturally occurring signal sequence is used to produce the fusion protein of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

[1187] The amplified fragment encoding the fusion protein of the invention is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[1188] The amplified fragment encoding the albumin fusion protein of the invention is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

[1189] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about

10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired fusion protein is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 28: [^{3}H]-2-Deoxyglucose Uptake Assay

[1190] Adipose, skeletal muscle, and liver are insulin-sensitive tissues. Insulin can stimulate glucose uptake/transport into these tissues. In the case of adipose and skeletal muscle, insulin initiates the signal transduction that eventually leads to the translocation of the glucose transporter 4 molecule, GLUT4, from a specialized intracellular compartment to the cell surface. Once on the cell surface, GLUT4 allows for glucose uptake/transport.

[^{3}H]-2-Deoxyglucose Uptake

[1191] A number of adipose and muscle related cell-lines can be used to test for glucose uptake/transport activity in the absence or presence of a combination of any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. In particular, the 3T3-L1 murine fibroblast cells and the L6 murine skeletal muscle cells can be differentiated into 3T3-L1 adipocytes and into myotubes, respectively, to serve as appropriate *in vitro* models for the [^{3}H]-2-deoxyglucose uptake assay (Urso et al., J Biol Chem, 274(43): 30864-73 (1999); Wang et al., J Mol Endocrinol, 19(3): 241-8 (1997); Haspel et al., J Membr Biol, 169 (1): 45-53 (1999); Tsakiridis et al., Endocrinology, 136(10): 4315-22 (1995)). Briefly, 2 x 10^5 cells/100 µL of adipocytes or differentiated L6 cells are transferred to 96-well Tissue-Culture, "TC", treated, i.e., coated with 50 µg/mL of poly-L-lysine, plates in post-differentiation medium and are incubated overnight at 37 °C in 5% CO_2. The cells are first washed once with serum free low glucose DMEM medium and are then starved with 100 µL/well of the same medium and with 100 µL/well of either buffer or of a combination of any one or more of the therapeutic drugs listed for

the treatment of diabetes mellitus, for example, increasing concentrations of 1 nM, 10 nM, and 100 nM of the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) for 16 hours at 37 °C in the absence or presence of 1 nM insulin. The plates are washed three times with 100 µL/well of HEPES buffered saline. Insulin is added at 1 nM in HEPES buffered saline for 30 min at 37 °C in the presence of 10 µM labeled [^{3}H]-2-deoxyglucose (Amersham, #TRK672) and 10 µM unlabeled 2-deoxyglucose (SIGMA, D-3179). As control, the same conditions are carried out except in the absence of insulin. A final concentration of 10 µM cytochalasin B (SIGMA, C6762) is added at 100 µL/well in a separate well to measure the non-specific uptake. The cells are washed three times with HEPES buffered saline. Labeled, i.e., 10 µM of [^{3}H]-2-deoxyglucose, and unlabeled, i.e., 10 µM of 2-deoxyglucose, are added for 10 minutes at room temperature. The cells are washed three times with cold Phosphate Buffered *Sal* ine, "PBS". The cells are lysed upon the addition of 150 µL/well of 0.2 N NaOH and subsequent incubation with shaking for 20 minutes at room temperature. Samples are then transferred to a scintillation vial to which is added 5 mL of scintillation fluid. The vials are counted in a Beta-Scintillation counter. Uptake in duplicate conditions, the difference being the absence or presence of insulin, is determined with the following equation: [(Insulin counts per minute "cpm" – Non-Specific cpm)/(No Insulin cpm – Non-Specific cpm)]. Average responses fall within the limits of about 5-fold and 3-fold that of controls for adipocytes and myotubes, respectively.

Differentiation of Cells

[1192] The cells are allowed to become fully confluent in a T-75 cm^2 flask. The medium is removed and replaced with 25 mL of pre-differentiation medium for 48 hours. The cells are incubated at 37 °C, in 5% CO_2, 85% humidity. After 48 hours, the pre-differentiation medium is removed and replaced with 25 mL differentiation medium for 48 hours. The cells are again incubated at 37 °C, in 5% CO_2, 85% humidity. After 48 hours, the medium is removed and replaced with 30 mL post-differentiation medium. Post-differentiation medium is maintained for 14-20 days or until complete differentiation is achieved. The medium is changed every 2-3 days. Human adipocytes can be purchased from Zen-Bio, INC (# SA-1096).

Example 29: *In Vitro* Assay Of [^{3}H]-Thymidine Incorporation Into Pancreatic Cell-Lines

[1193] It has recently been shown that GLP-1 induces differentiation of the rat pancreatic ductal epithelial cell-line ARIP in a time- and dose-dependent manner which is associated with an increase in Islet Duodenal Homeobox-1 (IDX-1) and insulin mRNA levels (Hui et al., Diabetes, 50(4): 785-96 (2001)). The IDX-1 in turn increases mRNA levels of the GLP-1 receptor.

Cells Types Tested

[1194] RIN-M cells: These cells are available from the American Type Tissue Culture Collection (ATCC Cell Line Number CRL-2057). The RIN-M cell line was derived from a radiation induced transplantable rat islet cell tumor. The line was established from a nude mouse xenograft of the tumor. The cells produce and secrete islet polypeptide hormones, and produce L-dopa decarboxylase (a marker for cells having amine precursor uptake and decarboxylation, or APUD, activity).

[1195] ARIP cells: These are pancreatic exocrine cells of epithelial morphology available from the American Type Tissue Culture Collection (ATCC Cell Line Number CRL-1674). See also, references: Jessop, N.W. and Hay, R.J., "Characteristics of two rat pancreatic exocrine cell lines derived from transplantable tumors," In Vitro 16: 212, (1980); Cockell, M. et al., "Identification of a cell-specific DNA-binding activity that interacts with a transcriptional activator of genes expressed in the acinar pancreas," Mol. Cell. Biol. 9: 2464-2476, (1989); Roux, E., et al. "The cell-specific transcription factor PTF1 contains two different subunits that interact with the DNA" Genes Dev. 3: 1613-1624, (1989); and, Hui, H., et al., "Glucagon-like peptide 1 induces differentiation of islet duodenal homeobox-1-positive pancreatic ductal cells into insulin-secreting cells," Diabetes 50: 785-796 (2001).

Preparation of Cells

[1196] The RIN-M cell-line is grown in RPMI 1640 medium (Hyclone, #SH300027.01) with 10% fetal bovine serum (HyClone, #SH30088.03) and is subcultured every 6 to 8 days at a ratio of 1:3 to 1:6. The medium is changed every 3 to 4 days.

[1197] The ARIP (ATCC #CRL-1674) cell-line is grown in Ham's F12K medium (ATCC, #30-2004) with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium

bicarbonate and 10% fetal bovine serum. The ARIP cell-line is subcultured at a ratio of 1:3 to 1:6 twice per week. The medium is changed every 3 to 4 days.

Assay Protocol

[1198] The cells are seeded at 4000 cells/well in 96-well plates and cultured for 48 to 72 hours to 50% confluence. The cells are switched to serum-free media at 100 μL/well. After incubation for 48-72 hours, serum and/or the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) are added to the well. Incubation persists for an additional 36 hours. [^{3}H]-Thymidine (5-20 Ci/mmol) (Amersham Pharmacia, #TRK120) is diluted to 1 microCuries/5 microliters. After the 36 hour incubation, 5 microliters is added per well for a further 24 hours. The reaction is terminated by washing the cells gently with cold Phosphate-Buffered *Sal* ine, "PBS", once. The cells are then fixed with 100 microliters of 10% ice cold TCA for 15 min at 4 °C. The PBS is removed and 200 microliters of 0.2 N NaOH is added. The plates are incubated for 1 hour at room temperature with shaking. The solution is transferred to a scintillation vial and 5 mL of scintillation fluid compatible with aqueous solutions is added and mixed vigorously. The vials are counted in a beta scintillation counter. As negative control, only buffer is used. As a positive control fetal calf serum is used.

Example 30: Assaying For Glycosuria

[1199] Glycosuria (i.e., excess sugar in the urine), can be readily assayed to provide an index of the disease state of diabetes mellitus. Excess urine in a patient sample as compared with a normal patient sample is symptomatic of IDDM and NIDDM. Efficacy of treatment of such a patient having IDDM and NIDDM is indicated by a resulting decrease in the amount of excess glucose in the urine. In a preferred embodiment for IDDM and NIDDM monitoring, urine samples from patients are assayed for the presence of glucose using techniques known in the art. Glycosuria in humans is defined by a urinary glucose concentration exceeding 100 mg per 100 ml. Excess sugar levels in those patients exhibiting glycosuria can be measured even more precisely by obtaining blood samples and assaying serum glucose.

Example 31: Occurrence Of Diabetes In Nod Mice

[1200] Female NOD (non-obese diabetic) mice are characterized by displaying IDDM with a course which is similar to that found in humans, although the disease is more pronounced in female than male NOD mice. Hereinafter, unless otherwise stated, the term "NOD mouse" refers to a female NOD mouse. NOD mice have a progressive destruction of beta cells which is caused by a chronic autoimmune disease. Thus, NOD mice begin life with euglycemia, or normal blood glucose levels. By about 15 to 16 weeks of age, however, NOD mice start becoming hyperglycemic, indicating the destruction of the majority of their pancreatic beta cells and the corresponding inability of the pancreas to produce sufficient insulin. Thus, both the cause and the progression of the disease are similar to human IDDM patients.

[1201] *In vivo* assays of efficacy of the immunization regimens can be assessed in female NOD/LtJ mice (commercially available from The Jackson Laboratory, Bar Harbor, Me.). In the literature, it's reported that 80% of female mice develop diabetes by 24 weeks of age and onset of insulitis begins between 6-8 weeks age. NOD mice are inbred and highly responsive to a variety of immunoregulatory strategies. Adult NOD mice (6-8 weeks of age) have an average mass of 20-25 g.

[1202] These mice can be either untreated (control), treated with the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof), alone or in combination with other therapeutic compounds stated above. The effect of these various treatments on the progression of diabetes can be measured as follows:

[1203] At 14 weeks of age, the female NOD mice can be phenotyped according to glucose tolerance. Glucose tolerance can be measured with the intraperitoneal glucose tolerance test (IPGTT). Briefly, blood is drawn from the paraorbital plexus at 0 minutes and 60 minutes after the intraperitoneal injection of glucose (1 g/kg body weight). Normal tolerance is defined as plasma glucose at 0 minutes of less than 144 mg %, or at 60 minutes of less than 160 mg %. Blood glucose levels are determined with a Glucometer Elite apparatus.

[1204] Based upon this phenotypic analysis, animals can be allocated to the different experimental groups. In particular, animals with more elevated blood glucose levels can be assigned to the impaired glucose tolerance group. The mice can be fed ad libitum and can

be supplied with acidified water (pH 2.3).

[1205] The glucose tolerant and intolerant mice can be further subdivided into control, albumin fusion proteins of the subject invention, and albumin fusion proteins/therapeutic compounds combination groups. Mice in the control group can receive an interperitoneal injection of vehicle daily, six times per week. Mice in the albumin fusion group can receive an interperitoneal injection of the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) in vehicle daily, six times per week. Mice in the albumin fusion proteins/therapeutic compounds combination group can receive both albumin fusion proteins and combinations of therapeutic compounds as described above.

[1206] The level of urine glucose in the NOD mice can be determined on a bi-weekly basis using Labstix (Bayer Diagnostics, Hampshire, England). Weight and fluid intake can also be determined on a bi-weekly basis. The onset of diabetes is defined after the appearance of glucosuria on two consecutive determinations. After 10 weeks of treatment, an additional IPGTT can be performed and animals can be sacrificed the following day.

[1207] Over the 10 week course of treatment, control animals in both the glucose tolerant and glucose intolerant groups develop diabetes at a rate of 60% and 86%, respectively (see US patent No. 5,866,546, Gross et al.). Thus, high rates of diabetes occur even in NOD mice which are initially glucose tolerant if no intervention is made.

[1208] Results can be confirmed by the measurement of blood glucose levels in NOD mice, before and after treatment. Blood glucose levels are measured as described above in both glucose tolerant and intolerant mice in all groups described.

[1209] In an alternative embodiment, the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) can be quantified using spectrometric analysis and appropriate protein quantities can be resuspended prior to injection in 50 .mu.l phosphate buffered saline (PBS) per dose. Two injections, one week apart, can be administered subcutaneously under the dorsal skin of each mouse. Monitoring can be performed on two separate occasions prior to immunization and can be performed weekly throughout the treatment and continued thereafter. Urine can be tested for glucose every week (Keto-Diastix.RTM.; Miles Inc., Kankakee, Ill.) and glycosuric mice can be checked for serum glucose (ExacTech.RTM.,

MediSense, Inc., Waltham, Mass.). Diabetes is diagnosed when fasting glycemia is greater than 2.5g/L.

Example 32: Histological Examination Of Nod Mice

[1210] Histological examination of tissue samples from NOD mice can demonstrate the ability of the compositions of the present invention, and/or a combination of the compositions of the present invention with other therapeutic agents for diabetes, to increase the relative concentration of beta cells in the pancreas. The experimental method is as follows:

[1211] The mice from Example 31 can be sacrificed at the end of the treatment period and tissue samples can be taken from the pancreas. The samples can be fixed in 10% formalin in 0.9% saline and embedded in wax. Two sets of 5 serial 5 .mu.m sections can be cut for immunolabelling at a cutting interval of 150 .mu.m. Sections can be immunolabelled for insulin (guinea pig anti-insulin antisera dilution 1:1000, ICN Thames U.K.) and glucagon (rabbit anti-pancreatic glucagon antisera dilution 1:2000) and detected with peroxidase conjugated anti-guinea pig (Dako, High Wycombe, U.K.) or peroxidase conjugated anti-rabbit antisera (dilution 1:50, Dako).

[1212] The composition of the present invention may or may not have as strong an effect on the visible mass of beta cells as it does on the clinical manifestations of diabetes in glucose tolerant and glucose intolerant animals.

Example 33: Pancreatic Beta-Cell Transplantation Combination Therapy

[1213] Transplantation is a common form of treatment of autoimmune disease, especially when the target self tissue has been severely damaged. For example, and not by way of limitation, pancreas transplantation and islet cell transplantation are common treatment options for IDDM (See, e.g., Stewart et al., Journal of Clinical Endocrinology & Metabolism 86 (3): 984-988 (2001); Brunicardi, Transplant. Proc. 28: 2138-40 (1996); Kendall & Robertson, Diabetes Metab. 22: 157-163 (1996); Hamano et al., Kobe J. Med. Sci. 42: 93-104 (1996); Larsen & Stratta, Diabetes Metab. 22: 139-146 (1996); and Kinkhabwala, et al., Am. J. Surg. 171: 516-520 (1996)). As with any transplantation method, transplantation therapies for autoimmune disease patients include treatments to

minimize the risk of host rejection of the transplanted tissue. However, autoimmune disease involves the additional, independent risk that the pre-existing host autoimmune response which damaged the original self tissue will exert the same damaging effect on the transplanted tissue. Accordingly, the present invention encompasses methods and compositions for the treatment of autoimmune pancreatic disease using the albumin fusion proteins of the subject invention in combination with immunomodulators/immunosuppressants in individuals undergoing transplantation therapy of the autoimmune disease.

[1214] In accordance with the invention, the albumin fusion-based compositions and formulations described above, are administered to prevent and treat damage to the transplanted organ, tissue, or cells resulting from the host individual's autoimmune response initially directed against the original self tissue. Administration may be carried out both prior and subsequent to transplantation in 2 to 4 doses each one week apart.

[1215] The following immunomodulators/immunosuppressants including, but not limited to, AI-401, CDP-571 (anti-TNF monoclonal antibody), CG-1088, Diamyd (diabetes vaccine), ICM3 (anti-ICAM-3 monoclonal antibody), linomide (Roquinimex), NBI-6024 (altered peptide ligand), TM-27, VX-740 (HMR-3480), caspase 8 protease inhibitors, thalidomide, hOKT3gamma1 (Ala-ala) (anti-CD3 monoclonal antibody), Oral Interferon-Alpha, oral lactobacillus, and LymphoStat-B™ can be used together with the albumin fusion therapeutics of the subject invention in islet cell or pancreas transplantation.

Example 34: *In Vivo* Mouse Model Of NIDDM

[1216] Male C57BL/6J mice from Jackson Laboratory (Bar Harbor, ME) can be obtained at 3 weeks of age and fed on conventional chow or diets enriched in either fat (35.5% wt/wt; Bioserv.Frenchtown, NJ) or fructose (60% wt/wt; Harlan Teklad, Madison, WI). The regular chow is composed of 4.5% wt/wt fat, 23% wt/wt protein, 31.9% wt/wt starch, 3.7% wt/wt fructose, and 5.3% wt/wt fiber. The high-fat (lard) diet is composed of 35.5% wt/wt fat, 20% wt/wt protein, 36.4% wt/wt starch, 0.0% wt/wt fructose, and 0.1% wt/wt fiber. The high-fructose diet is composed of 5% wt/wt fat, 20% wt/wt protein, 0.0% wt/wt starch, 60% wt/wt fructose, and 9.4% wt/wt fiber. The mice may be housed no more than five per cage at 22° +/- 3°C temperature- and 50% +/- 20% humidity-controlled

room with a 12-hour light (6 am to 6 pm)/dark cycle (Luo et al., Metabolism 47(6): 663-8 (1998), "Nongenetic mouse models of non-insulin-dependent diabetes mellitus"; Larsen et al., Diabetes 50(11): 2530-9 (2001), "Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats"). After exposure to the respective diets for 3 weeks, mice can be injected intraperitoneally with either streptozotocin, "STZ" (Sigma, St. Louis, MO), at 100 mg/kg body weight or vehicle (0.05 mol/L citric acid, pH 4.5) and kept on the same diet for the next 4 weeks. Under nonfasting conditions, blood is obtained 1, 2, and 4 weeks post-STZ by nipping the distal part of the tail. Samples are used to measure nonfasting plasma glucose and insulin concentrations. Body weight and food intake are recorded weekly.

[1217] To directly determine the effect of the high-fat diet on the ability of insulin to stimulate glucose disposal, the experiments can be initiated on three groups of mice, fat-fed, chow-fed injected with vehicle, and fat-fed injected with STZ at the end of the 7-week period described above. Mice can be fasted for 4 hours before the experiments. In the first series of experiments, mice can be anesthetized with methoxyflurane (Pitman-Moor, Mundelein, IL) inhalation. Regular insulin (Sigma) can be injected intravenously ([IV] 0.1 U/kg body weight) through a tail vein, and blood can be collected 3, 6, 9, 12, and 15 minutes after the injection from a different tail vein. Plasma glucose concentrations can be determined on these samples, and the half-life ($t_{1/2}$) of glucose disappearance from plasma can be calculated using WinNonlin (Scientific Consulting, Apex, NC), a pharmacokinetics/pharmacodynamics software program.

[1218] In the second series of experiments, mice can be anesthetized with intraperitoneal sodium pentobarbital (Sigma). The abdominal cavity is opened, and the main abdominal vein is exposed and catheterized with a 24-gauge IV catheter (Johnson-Johnson Medical, Arlington, TX). The catheter is secured to muscle tissue adjacent to the abdominal vein, cut on the bottom of the syringe connection, and hooked to a prefilled PE50 plastic tube, which in turn is connected to a syringe with infusion solution. The abdominal cavity is then sutured closed. With this approach, there would be no blockage of backflow of the blood from the lower part of the body. Mice can be infused continuously with glucose (24.1 mg/kg/min) and insulin (10 mU/kg/min) at an infusion volume of 10 μL/min. Retro-orbital blood samples (70 μL each) can be taken 90, 105,

120, and 135 minutes after the start of infusion for measurement of plasma glucose and insulin concentrations. The mean of these four samples is used to estimate steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations for each animal.

[1219] Finally, experiments to evaluate the ability of the albumin fusion proteins, the therapeutic compositions of the instant application, either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus, to decrease plasma glucose can be performed in the following two groups of "NIDDM" mice models that are STZ-injected: (1) fat-fed C57BL/6J, and (2) fructose-fed C57BL/6J. Plasma glucose concentrations of the mice for these studies may range from 255 to 555 mg/dL. Mice are randomly assigned to treatment with either vehicle, albumin fusion therapeutics of the present invention either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. A total of three doses can be administered. Tail vein blood samples can be taken for measurement of the plasma glucose concentration before the first dose and 3 hours after the final dose.

[1220] Plasma glucose concentrations can be determined using the Glucose Diagnostic Kit from Sigma (Sigma No. 315), an enzyme colorimetric assay. Plasma insulin levels can be determined using the Rat Insulin RIA Kit from Linco Research (#RI-13K; St. Charles, MO).

Example 35: *In Vitro* H4IIE –SEAP Reporter Assays Establishing Involvement In Insulin Action

The Various H4IIe Reporters

[1221] H4IIe/rMEP-SEAP: The malic enzyme promoter isolated from rat (rMEP) contains a PPAR-gamma element which is in the insulin pathway. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1222] H4IIe/SREBP-SEAP: The sterol regulatory element binding protein (SREBP-1c) is a transcription factor which acts on the promoters of a number of insulin-responsive genes, for example, fatty acid synthetase (FAS), and which regulates expression of key genes in fatty acid metabolism in fibroblasts, adipocytes, and hepatocytes. SREBP-1c, also known as the adipocyte determination and differentiation factor 1 (ADD-1), is considered as the primary mediator of insulin effects on gene

expression in adipose cells. It's activity is modulated by the levels of insulin, sterols, and glucose. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1223] H4IIe/FAS-SEAP: The fatty acid synthetase reporter constructs contain a minimal SREBP-responsive FAS promoter. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1224] H4IIe/PEPCK-SEAP: The phosphoenolpyruvate carboxykinase (PEPCK) promoter is the primary site of hormonal regulation of PEPCK gene transcription modulating PEPCK activity. PEPCK catalyzes a committed and rate-limiting step in hepatic gluconeogenesis and must therefore be carefully controlled to maintain blood glucose levels within normal limits. This reporter construct is stably transfected into the liver H4IIe cell-line.

[1225] These reporter constructs can also be stably transfected into 3T3-L1 fibroblasts and L6 myoblasts. These stable cell-lines are then differentiated into 3T3-L1 adipocytes and L6 myotubes as previously described in Example 28. The differentiated cell-lines can then be used in the SEAP assay described below.

Growth and Assay Medium

[1226] The growth medium comprises 10% Fetal Bovine Serum (FBS), 10% Calf Serum, 1% NEAA, 1x penicillin/streptomycin, and 0.75 mg/mL G418 (for H4IIe/rFAS-SEAP and H4IIe/SREBP-SEAP) or 0.50 mg/mL G418 (for H4IIe/rMEP-SEAP). For H4IIe/PEPCK-SEAP, the growth medium consists of 10% FBS, 1% penicillin/streptomycin, 15 mM HEPES buffered saline, and 0.50 mg/mL G418.

[1227] The assay medium consists of low glucose DMEM medium (Life Technologies), 1% NEAA, 1x penicillin/streptomycin for the H4IIe/rFAS-SEAP, H4IIe/SREBP-SEAP, H4IIe/rMEP-SEAP reporters. The assay medium for H4IIe/PEPCK-SEAP reporter consists of 0.1% FBS, 1% penicillin/streptomycin, and 15 mM HEPES buffered saline.

Method

[1228] The 96-well plates are seeded at 75,000 cells/well in 100 μL/well of growth medium until cells in log growth phase become adherent. Cells are starved for 48 hours by replacing growth medium with assay medium, 200 μL/well. (For H4IIe/PEPCK-SEAP cells, assay medium containing 0.5 μM dexamethasone is added at 100 μL/well and

incubated for approximately 20 hours). The assay medium is replaced thereafter with 100 µL/well of fresh assay medium, and a 50 µL aliquot of cell supernatant obtained from transfected cell-lines expressing the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) is added to the well. Supernatants from empty vector transfected cell-lines are used as negative control. Addition of 10 nM and/or 100 nM insulin to the wells is used as positive control. After 48 hours of incubation, the conditioned media are harvested and SEAP activity measured (Phospha-Light System protocol, Tropix #BP2500). Briefly, samples are diluted 1:4 in dilution buffer and incubated at 65 °C for 30 minutes to inactivate the endogenous non-placental form of SEAP. An aliquot of 50 µL of the diluted samples is mixed with 50 µL of SEAP Assay Buffer which contains a mixture of inhibitors active against the non-placental SEAP isoenzymes and is incubated for another 5 minutes. An aliquot of 50 µL of CSPD chemiluminescent substrate which is diluted 1:20 in Emerald luminescence enhancer is added to the mixture and incubated for 15-20 minutes. Plates are read in a Dynex plate luminometer.

Example 36: Preparation Of HA-Hormone Fusion Protein (Such As Insulin, GLP-1)

[1229] The cDNA for the hormone of interest such as insulin can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available, for instance, in public databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The hormone cDNA is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence

and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Example 37: Preparation Of HA-Soluble Receptor Or HA-Binding Protein Fusion Protein Such As HA-TNF Receptor

[1230] The cDNA for the soluble receptor or binding protein of interest such as TNF receptor can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available, for instance, in GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The receptor cDNA is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Example 38: Preparation Of HA-Growth Factors Such As HA-IGF-1 Fusion Protein

[1231] The cDNA for the growth factor of interest such as IGF-1 can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods (see GenBank Acc. No.NP_000609). The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The growth factor cDNA is cloned

into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA, or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Example 39: Preparation Of HA-Single Chain Antibody Fusion Proteins

[1232] Single chain antibodies are produced by several methods including but not limited to: selection from phage libraries, cloning of the variable region of a specific antibody by cloning the cDNA of the antibody and using the flanking constant regions as the primer to clone the variable region, or by synthesizing an oligonucleotide corresponding to the variable region of any specific antibody. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The cell cDNA is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA, or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast.

[1233] In fusion molecules of the invention, the V_H and V_L can be linked by one of the following means or a combination thereof: a peptide linker between the C-terminus of the V_H and the N-terminus of the V_L; a Kex2p protease cleavage site between the V_H and V_L such that the two are cleaved apart upon secretion and then self associate; and cysteine residues positioned such that the V_H and V_L can form a disulphide bond between them to link them together. An alternative option would be to place the V_H at the N-terminus of HA or an HA domain fragment and the V_L at the C-terminus of the HA or HA domain fragment.

[1234] The albumin fusion protein secreted from the yeast can then be collected and

purified from the media and tested for its activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines. The antibody produced in this manner can be purified from media and tested for its binding to its antigen using standard immunochemical methods.

Example 40: Preparation Of HA-Cell Adhesion Molecule Fusion Proteins

[1235] The cDNA for the cell adhesion molecule of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. . The nucleotide sequences for the known cell adhesion molecules are known and available, for instance, in GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The cell adhesion molecule cDNA is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA, or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Example 41: Preparation Of Inhibitory Factors And Peptides As HA Fusion Proteins (Such As HA-Antiviral, HA-Antibiotic, HA-Enzyme Inhibitor And HA-Anti-Allergic Proteins).

[1236] The cDNA for the peptide of interest such as an antibiotic peptide can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-

PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The peptide cDNA is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA, or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Example 42: Preparation Of Targeted HA Fusion Proteins.

[1237] The cDNA for the protein of interest can be isolated from cDNA library or can be made synthetically using several overlapping oligonucleotides using standard molecular biology methods. The appropriate nucleotides can be engineered in the cDNA to form convenient restriction sites and also allow the attachment of the protein cDNA to albumin cDNA similar to the method described for hGH. Also a targeting protein or peptide cDNA such as single chain antibody or peptides, such as nuclear localization signals, that can direct proteins inside the cells can be fused to the other end of albumin. The protein of interest and the targeting peptide is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA , or pC4:HSA which allows the fusion with albumin cDNA. In this manner both N- and C-terminal end of albumin are fused to other proteins. The fused cDNA is then excised from pPPC0005 and is inserted into a plasmid such as pSAC35 to allow the expression of the albumin fusion protein in yeast. All the above procedures can be performed using standard methods in molecular biology. The albumin fusion protein secreted from yeast can be collected and purified from the media and tested for its biological activity and its targeting activity using appropriate biochemical and biological tests.

Example 43: Preparation Of HA-Enzymes Fusions.

[1238] The cDNA for the enzyme of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The enzyme cDNA is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Example 44: Bacterial Expression Of An Albumin Fusion Protein.

[1239] A polynucleotide encoding an albumin fusion protein of the present invention comprising a bacterial signal sequence is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, to synthesize insertion fragments. The primers used to amplify the polynucleotide encoding insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

[1240] The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment

is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^R). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

[1241] Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

[1242] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl or preferably in 8 M urea and concentrations greater than 0.14 M 2-mercaptoethanol by stirring for 3-4 hours at 4°C (see, e.g., Burton et al., Eur. J. Biochem. *179*:379-387 (1989)). The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

[1243] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8. The column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

[1244] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. Exemplary conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation

the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

[1245] In addition to the above expression vector, the present invention further includes an expression vector, called pHE4a (ATCC Accession Number 209645, deposited on February 25, 1998) which contains phage operator and promoter elements operatively linked to a polynucleotide encoding an albumin fusion protein of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter and operator sequences are made synthetically.

[1246] DNA can be inserted into the pHE4a by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to PCR protocols described herein or otherwise known in the art, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

[1247] The engineered vector may be substituted in the above protocol to express protein in a bacterial system.

Example 45: Multifusion Fusions

[1248] Albumin fusion proteins of the invention containing multiple Therapeutic protein portions fused at the N- and C- termini of albumin may include, but are not limited to, GLP1-HSA-GLP-1, GLP1-HSA-Exendin 4, Exendin 4-HSA-Exendin 4, Exendin 4-HSA-GLP1, GLP1-HSA-Insulin, Exendin 4-HSA-Insulin, Insulin-HSA-Insulin, Insulin-HSA-GLP1, Insulin-HSA-Exendin 4, GLP1-HSA-Resistin, Exendin 4-HSA-Resistin, Insulin-HSA-Resistin, Resistin-HSA-Resistin, Resistin-HSA-GLP1, Resistin-HSA-Exendin 4, Resistin-HSA-Insulin, GLP1-HSA-Leptin, Exendin 4-HSA-Leptin, Insulin-

HSA-Leptin, Resistin-HSA-Leptin, Leptin-HSA-Leptin, Leptin-HSA-GLP1, Leptin-HSA-Exendin 4, Leptin-HSA-Insulin, Leptin-HSA-Resistin, GLP1-HSA-IGF1, IGF1-HSA-IGF1, Exendin 4-HSA-IGF1, Insulin-HSA-IGF1, Resistin-HSA–IGF1, Leptin-HSA–IGF1, IGF1-HSA-GLP1, IGF1-HSA-Exendin 4, IGF1-HSA-Insulin, IGF1-HSA-Resistin, IGF1-HSA-Leptin, HCEIP80-HSA-HCEIP80, IGF1-HSA-HCEIP80, GLP1-HSA-HCEIP80, Exendin 4-HSA-HCEIP80, Insulin-HSA-HCEIP80, Resistin-HSA-HCEIP80, Leptin-HSA-HCEIP80, HCEIP80-HSA-IGF1, HCEIP80-HSA-GLP1, HCEIP80-HSA-Exendin 4, HCEIP80-HSA-Insulin, HCEIP80-HSA-Resistin, HCEIP80-HSA-Leptin, HCEIP80-HSA-HLDOU18, IGF1-HSA-HLDOU18, GLP1-HSA-HLDOU18, Exendin 4-HSA-HLDOU18, Insulin-HSA-HLDOU18, Resistin-HSA-HLDOU18, Leptin-HSA-HLDOU18, HLDOU18-HSA-HCEIP80, HLDOU18-HSA-IGF1, HLDOU18-HSA-GLP1, HLDOU18-HSA-Exendin 4, HLDOU18-HSA-Insulin, HLDOU18-HSA-Resistin, HLDOU18-HSA-Leptin, and HLDOU18-HSA-HLDOU18, HCEIP80-HSA-RegIV, IGF1-HSA-RegIV, GLP1-HSA-RegIV, Exendin 4-HSA-RegIV, Insulin-HSA-RegIV, Resistin-HSA-RegIV, Leptin-HSA-RegIV, HLDOU18-HSA-RegIV, RegIV-HSA-HCEIP80, RegIV-HSA-IGF1, RegIV-HSA-GLP1, RegIV-HSA-Exendin 4, RegIV-HSA-Insulin, RegIV-HSA-Resistin, RegIV-HSA-Leptin, RegIV-HSA-HLDOU18, RegIV-HSA-RegIV, HCEIP80-HSA-HDRMI82, IGF1-HSA-HDRMI82, GLP1-HSA-HDRMI82, Exendin 4-HSA-HDRMI82, Insulin-HSA-HDRMI82, Resistin-HSA-HDRMI82, Leptin-HSA-HDRMI82, HLDOU18-HSA-HDRMI82, RegIV-HSA-HDRMI82, HDRMI82-HSA-HCEIP80, HDRMI82-HSA-IGF1, HDRMI82-HSA-GLP1, HDRMI82-HSA-Exendin 4, HDRMI82-HSA-Insulin, HDRMI82-HSA-Resistin, HDRMI82-HSA-Leptin, HDRMI82-HSA-HLDOU18, HDRMI82-HSA-RegIV, HDRMI82-HSA-HDRMI82, HCEIP80-HSA-IFNa, IGF1-HSA-IFNa, GLP1-HSA-IFNa, Exendin 4-HSA-IFNa, Insulin-HSA-IFNa, Resistin-HSA-IFNa, Leptin-HSA-IFNa, HLDOU18-HSA-IFNa, RegIV-HSA-IFNa, HDRMI82-HSA-IFNa, IFNa-HSA-HCEIP80, IFNa-HSA-IGF1, IFNa-HSA-GLP1, IFNa-HSA-Exendin 4, IFNa-HSA-Insulin, IFNa-HSA-Resistin, IFNa-HSA-Leptin, IFNa-HSA-HLDOU18, IFNa-HSA-RegIV, IFNa-HSA-HDRMI82, and IFNa-HSA-IFNa.

[1249] The albumin fusion proteins (e.g,. containing a Therapeutic protein (or fragment or variant thereof) fused to albumin (or a fragment or variant thereof)) may additionally be fused to other proteins to generate "multifusion proteins". These multifusion proteins can

be used for a variety of applications. For example, fusion of the albumin fusion proteins of the invention to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See e.g,. EP A 394,827; Traunecker et al., Nature 331:84-86 (1988)). Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of an albumin fusion protein. Furthermore, the fusion of additional protein sequences to the albumin fusion proteins of the invention may further increase the solubility and/or stability of the fusion protein. The fusion proteins described above can be made using or routinely modifying techniques known in the art and/or by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule.

[1250] Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian or yeast expression vector.

[1251] For example, if pC4 (ATCC Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide encoding an albumin fusion protein of the present invention (generated and isolated using techniques known in the art), is ligated into this BamHI site. Note that the polynucleotide encoding the fusion protein of the invention is cloned without a stop codon, otherwise a Fc containing fusion protein will not be produced.

[1252] If the naturally occurring signal sequence is used to produce the albumin fusion protein of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCA
GCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA

GGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACG
TAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGA
GGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC
CGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGA
GTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACC
ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC
CATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA
AGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC
TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAG
CCTCTCCCTGTCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT
(SEQ ID NO: 397)

Example 46: Production Of An Antibody From An Albumin Fusion Protein.

a)Hybridoma Technology

[1253] Antibodies that bind the albumin fusion proteins of the present invention and portions of the albumin fusion proteins of the present invention (e.g., the Therapeutic protein portion or albumin portion of the fusion protein) can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, a preparation of an albumin fusion protein of the invention or a portion of an albumin fusion protein of the invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

[1254] Monoclonal antibodies specific for an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, are prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention. The splenocytes of such mice

are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention.

[1255] Alternatively, additional antibodies capable of binding to an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the an albumin fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibody can be blocked by the fusion protein of the invention, or a portion of an albumin fusion protein of the invention. Such antibodies comprise anti-idiotypic antibodies to the fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibody and are used to immunize an animal to induce formation of further fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibodies.

[1256] For *in vivo* use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., International Publication No. WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268

(1985)).

b) Isolation Of Antibody Fragments Directed Against an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention From A Library Of scFvs

[1257] Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

c) Rescue of the Library.

[1258] A library of scFvs is constructed from the RNA of human PBLs as described in International Publication No. WO 92/01047. To rescue phage displaying antibody fragments, approximately 10^9 *E. coli* harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see International Publication No. WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in International Publication No. WO 92/01047.

[1259] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium

by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10^{13} transducing units/ml (ampicillin-resistant clones).

Panning of the Library.

[1260] Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10^{13} TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders.

[1261] Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., International Publication No. WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 47: Method Of Treatment Using Gene Therapy-*Ex Vivo*.

[1262] One method of gene therapy transplants fibroblasts, which are capable of expressing an albumin fusion protein of the present invention, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

[1263] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

[1264] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[1265] Polynucleotides encoding an albumin fusion protein of the invention can be generated using techniques known in the art amplified using PCR primers which correspond to the 5' and 3' end sequences and optionally having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

[1266] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10%

calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

[1267] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether the albumin fusion protein is produced.

[1268] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 48: Method of Treatment Using Gene Therapy - *In Vivo*.

[1269] Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences encoding an albumin fusion protein of the invention into an animal. Polynucleotides encoding albumin fusion proteins of the present invention may be operatively linked to (i.e., associated with) a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

[1270] The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[1271] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, polynucleotides encoding albumin fusion proteins of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

[1272] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[1273] The polynucleotide construct can be delivered to the interstitial space of tissues within an animal, including muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are

preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[1274] For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[1275] The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[1276] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[1277] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for fusion protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 49: Transgenic Animals

[1278] The albumin fusion proteins of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express fusion proteins of the invention in humans, as part of a gene therapy protocol.

[1279] Any technique known in the art may be used to introduce the polynucleotides encoding the albumin fusion proteins of the invention into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-

229 (1989), which is incorporated by reference herein in its entirety.

[1280] Any technique known in the art may be used to produce transgenic clones containing polynucleotides encoding albumin fusion proteins of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

[1281] The present invention provides for transgenic animals that carry the polynucleotides encoding the albumin fusion proteins of the invention in all their cells, as well as animals which carry these polynucleotides in some, but not all their cells, *i.e.,* mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.,* head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide encoding the fusion protein of the invention be integrated into the chromosomal site of the endogenous gene corresponding to the Therapeutic protein portion or ablumin portion of the fusion protein of the invention, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

[1282] Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to

verify that integration of the polynucleotide encoding the fusion protein of the invention has taken place. The level of mRNA expression of the polynucleotide encoding the fusion protein of the invention in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of fusion protein-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the fusion protein.

[1283] Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene (i.e., polynucleotide encoding an albumin fusion protein of the invention) on a distinct background that is appropriate for an experimental model of interest.

[1284] Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of fusion proteins of the invention and the Therapeutic protein and/or albumin component of the fusion protein of the invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in treating (e.g., ameliorating) such conditions and/or disorders.

Example 50: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation.

[1285] Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may

impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

[1286] One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

[1287] *In Vitro* Assay- Albumin fusion proteins of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin) can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of an albumin fusion protein of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

[1288] Various dilutions of each sample are placed into individual wells of a 96-well

plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5 X 10^{-5}M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

[1289] *In vivo* Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of an albumin fusion protein of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin). Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with the albumin fusion protein of the invention identify the results of the activity of the fusion protein on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

[1290] Flow cytometric analyses of the spleens from mice treated with the albumin fusion protein is used to indicate whether the albumin fusion protein specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

[1291] Likewise, a predicted consequence of increased mature B-cell representation *in vivo* is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and fusion protein treated mice.

[1292] The studies described in this example tested activity of fusion proteins of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of fusion proteins and polynucleotides of the invention (e.g., gene therapy).

Example 51: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models.

Diabetic db+/db+ Mouse Model.

[1293] To demonstrate that an albumin fusion protein of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al., J. Surg. Res. 52*:389 (1992); Greenhalgh, D.G. *et al., Am. J. Pathol. 136*:1235 (1990)).

[1294] The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al. Proc. Natl. Acad. Sci. USA 77*:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al., J. Immunol. 120*:1375 (1978); Debray-Sachs, M. *et al., Clin. Exp. Immunol. 51(1)*:1-7 (1983); Leiter *et al., Am. J. of Pathol. 114*:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al., Exp. Neurol. 83(2)*:221-232 (1984); Robertson *et al., Diabetes 29(1)*:60-67 (1980); Giacomelli *et al., Lab Invest. 40(4)*:460-473 (1979); Coleman, D.L., *Diabetes 31 (Suppl)*:1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al., J. Immunol. 120*:1375-1377 (1978)).

[1295] The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al., Am. J. of Pathol. 136*:1235-1246 (1990)).

[1296] Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All

manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[1297] Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med. 172*:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[1298] Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[1299] An albumin fusion protein of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

[1300] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[1301] Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

[1302] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by

establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm^2, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

[1303] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an albumin fusion protein of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al., Am. J. Pathol. 136:*1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

[1304] Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

[1305] Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

[1306] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

Steroid Impaired Rat Model

[1307] The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl*et al., J. Immunol. 115*: 476-481 (1975); Werb *et al., J. Exp. Med. 147*:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al., An. Intern. Med. 37*:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., *J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In:* Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In*: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al., Proc. Natl. Acad. Sci. USA 86*: 2229-2233 (1989)).

[1308] To demonstrate that an albumin fusion protein of the invention can accelerate the healing process, the effects of multiple topical applications of the fusion protein on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

[1309] Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[1310] The wounding protocol is followed according to that described above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50

mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[1311] Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[1312] The fusion protein of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

[1313] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[1314] Three groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

[1315] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

[1316] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks

are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an albumin fusion protein of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

[1317] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

[1318] The studies described in this example tested activity of an albumin fusion protein of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of fusion proteins and polynucleotides of the invention (e.g., gene therapy).

Example 52: Lymphedema Animal Model.

[1319] The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an albumin fusion protein of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

[1320] Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

[1321] Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

[1322] Using a microscope, muscles in back of the leg (near the semitendinosis and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

[1323] Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

[1324] To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect of plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

[1325] Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people and those 2 readings are averaged. Readings are taken from both control and edematous limbs.

[1326] Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), and both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in

water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

[1327] Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and $Ca2^+$ comparison.

[1328] Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

[1329] Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

[1330] The studies described in this example tested activity of fusion proteins of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of fusion protein and polynucleotides of the invention (e.g., gene therapy).

Example 53: T Cell Proliferation Assay.

[1331] A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^{3}H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10^4/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of an albumin fusion protein of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin) (total volume 200 ul). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 µl of supernatant is removed and stored –20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 ul of

medium containing 0.5 uCi of ^{3}H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of ^{3}H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative control for the effects of fusion proteins of the invention.

Example 54: Effect of Fusion Proteins of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells.

[1332] Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-α, causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FCγRII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

[1333] FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of an albumin fusion protein of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[1334] Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^{6}/ml) are treated with increasing concentrations of an albumin

fusion protein of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

[1335] Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increased expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

[1336] FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of an albumin fusion protein of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[1337] Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Albumin fusion proteins of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

[1338] Monocyte Survival Assay. Human peripheral blood monocytes progressively

lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated processes (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the fusion protein to be tested. Cells are suspended at a concentration of 2 x 10^6/ml in PBS containing PI at a final concentration of 5 μg/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

[1339] Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of 5x10^5 cells/ml with increasing concentrations of an albumin fusion protein of the invention and under the same conditions, but in the absence of the fusion protein. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in the presence of the fusion protein. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

[1340] Oxidative burst. Purified monocytes are plated in 96-w plate at 2-1x10^5 cell/well. Increasing concentrations of an albumin fusion protein of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is

stopped by adding 20 μl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H_2O_2 produced by the macrophages, a standard curve of a H_2O_2 solution of known molarity is performed for each experiment.

Example 55: Biological Effects of Fusion Proteins of the Invention.

Astrocyte and Neuronal Assays.

[1341] Albumin fusion proteins of the invention can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an albumin fusion protein of the invention's activity on these cells.

[1342] Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA 83*:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an albumin fusion protein of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays.

[1343] Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human

lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test fusion protein of the invention proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE_2 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or fusion protein of the invention with or without IL-1α for 24 hours. The supernatants are collected and assayed for PGE_2 by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without an albumin fusion protein of the invention and/or IL-1α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

[1344] Human lung fibroblasts are cultured with FGF-2 or an albumin fusion protein of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with the fusion protein of the invention.

Cell proliferation based on [3H]thymidine incorporation

[1345] The following [3H]Thymidine incorporation assay can be used to measure the effect of a Therapeutic proteins, e.g., growth factor proteins, on the proliferation of cells such as fibroblast cells, epithelial cells or immature muscle cells.

[1346] Sub-confluent cultures are arrested in G1 phase by an 18 h incubation in serum-free medium. Therapeutic proteins are then added for 24 h and during the last 4 h, the cultures are labeled with [3H]thymidine, at a final concentration of 0.33 μM (25 Ci/mmol, Amersham, Arlington Heights, IL). The incorporated [3H]thymidine is precipitated with ice-cold 10% trichloroacetic acid for 24 h. Subsequently, the cells are rinsed sequentially with ice-cold 10% trichloroacetic acid and then with ice-cold water. Following lysis in 0.5

M NaOH, the lysates and PBS rinses (500 ml) are pooled, and the amount of radioactivity is measured.

Parkinson Models.

[1347] The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP^+) and released. Subsequently, MPP^+ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP^+ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotidamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

[1348] It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

[1349] Based on the data with FGF-2, an albumin fusion protein of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an albumin fusion protein of the invention is first examined in vitro in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm^2 on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed

with paraformaldehyde after 8 days in vitro and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

[1350] Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a therapeutic protein of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the fusion protein may be involved in Parkinson's Disease.

Example 56: The Effect of Albumin Fusion Proteins of the Invention on the Growth of Vascular Endothelial Cells.

[1351] On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2-5x10^4 cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnique, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An albumin fusion protein of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

[1352] An increase in the number of HUVEC cells indicates that the fusion protein may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cells indicates that the fusion protein inhibits vascular endothelial cells.

Example 57: Rat Corneal Wound Healing Model.

[1353] This animal model shows the effect of an albumin fusion protein of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

Inserting a spatula below the lip of the incision facing the outer corner of the eye.

Making a pocket (its base is 1-1.5 mm form the edge of the eye).

Positioning a pellet, containing 50ng- 5ug of an albumin fusion protein of the invention, within the pocket.

[1354] Treatment with an an albumin fusion protein of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

Example 58: Suppression of TNF alpha-Induced Adhesion Molecule Expression by an Albumin Fusion Protein of the Invention.

[1355] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[1356] Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

[1357] The potential of an albumin fusion protein of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

[1358] To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO_2.

HUVECs are seeded in 96-well plates at concentrations of 1 x 10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

[1359] Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca^{++} and Mg^{++}) is added to each well. Plates are held at 4°C for 30 min.

[1360] Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

[1361] Then add 20 μl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 μl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μl of pNNP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 μl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [

5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 59: Construction of GAS Reporter Construct

[1362] One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

[1363] GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

[1364] The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

[1365] The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995)). A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xaa-Trp-Ser (SEQ ID NO: 398)).

[1366] Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn

activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway (See Table 4, below). Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

Table 4

JAKs Ligand	tyk2	STATS Jak1	Jak2	Jak3	GAS(elements)or ISRE	
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g (IRF1>Lys6>IFP)		+	+	-	1	GAS
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotropic) GAS(IRF1>Lys6>IFP)	+	+	+	?	1,3	
Il-11(Pleiotropic)	?	+	?	?	1,3	
OnM(Pleiotropic)	?	+	+	?	1,3	
LIF(Pleiotropic)	?	+	+	?	1,3	
CNTF(Pleiotropic)	-/+	+	+	?	1,3	
G-CSF(Pleiotropic)	?	+	?	?	1,3	
IL-12(Pleiotropic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid) 6GAS(IRF1=IFP>>Ly6)(IgH)	-	+	-	+		
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid) GAS(IRF1>IFP>>Ly6)		-	-	+	-	5
IL-5 (myeloid) GAS		-	-	+	-	5
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO CAS>IRF1=IFP>>Ly6)	?	-	+	-	5 (B-	GAS
Receptor Tyrosine Kinases						
EGF GAS (IRF1)	?	+	+	-	1,3	
PDGF	?	+	+	-	1,3	
CSF-1 GAS(not IRF1)	?	+	+	-	1,3	

[1367] To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 62-64, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAA ATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO: 399)

[1368] The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:400)

[1369] PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGA TTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTA ACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCAT GGCTGACTAATTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAG CTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA GCTT:3' (SEQ ID NO:401)

[1370] With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

[1371] The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and

XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[1372] Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 62-64.

[1373] Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing EGR and NF-KB promoter sequences are described in Examples 62-66. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 60: Assay for SEAP Activity

[1374] As a reporter molecule for the assays described in examples disclosed herein, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

[1375] Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a solution containing an albumin fusion protein of the invention. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

[1376] Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5

min. Empty the dispenser and prime with the Reaction Buffer (see the Table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on a luminometer, thus one should treat 5 plates at each time and start the second set 10 minutes later.

[1377] Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Table 5

# of plates	Rxn buffer diluent (ml)	CSPD (ml)	# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3	31	165	8.25
11	65	3.25	32	170	8.5
12	70	3.5	33	175	8.75
13	75	3.75	34	180	9
14	80	4	35	185	9.25
15	85	4.25	36	190	9.5
16	90	4.5	37	195	9.75
17	95	4.75	38	200	10
18	100	5	39	205	10.25
19	105	5.25	40	210	10.5
20	110	5.5	41	215	10.75
21	115	5.75	42	220	11
22	120	6	43	225	11.25
23	125	6.25	44	230	11.5
24	130	6.5	45	235	11.75
25	135	6.75	46	240	12
26	140	7	47	245	12.25
27	145	7.25	48	250	12.5
28	150	7.5	49	255	12.75
29	155	7.75	50	260	13
30	160	8			

Example 61: Assay Identifying Neuronal Activity

[1378] When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, the ability of fusion proteins of the invention to activate cells can be assessed.

[1379] Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by an albumin fusion protein of the present invention can be assessed.

[1380] The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

First primer: 5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG-3' (SEQ ID NO: 402)

Second primer: 5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:403)

[1381] Using the GAS:SEAP/Neo vector produced in Example 59, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

[1382] To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

[1383] PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-

inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

[1384] Transfect the EGR/SEAP/Neo construct into PC12 using techniques known in the art. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

[1385] To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

[1386] The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

[1387] Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add a series of different concentrations of an albumin fusion protein of the inventon, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay may be routinely performed using techniques known in the art and/or as described in Example 60.

Example 62: Assay for T-cell Activity

[1388] The following protocol is used to assess T-cell activity by identifying factors, and determining whether an albumin fusion protein of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 59. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

[1389] Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate

stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

[1390] Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

[1391] During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

[1392] The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with varying concentrations of one or more fusion proteins of the present invention.

[1393] On the day of treatment with the fusion protein, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of fusion proteins and the number of different concentrations of fusion proteins being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

[1394] The well dishes containing Jurkat cells treated with the fusion protein are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 60. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

[1395] As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

[1396] The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 63: Assay for T-cell Activity

[1397] NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

[1398] In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

[1399] Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the fusion protein. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

[1400] To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:404), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTT
CCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:405)

[1401] The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO: 400)

[1402] PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATC TGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCC GCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTT TTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGT AGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:406)

[1403] Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[1404] In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

[1405] Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 60. Similarly, the method for assaying fusion proteins with these stable Jurkat T-cells is also described in Example 60. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 64: Assay Identifying Myeloid Activity

[1406] The following protocol is used to assess myeloid activity of an albumin fusion protein of the present invention by determining whether the fusion protein proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 59. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The

myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

[1407] To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 59, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest $2x10^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

[1408] Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37 degrees C for 45 min.

[1409] Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

[1410] The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

[1411] These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

[1412] Add different concentrations of the fusion protein. Incubate at 37 degee C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to methods known in the art and/or the protocol described in Example 60.

Example 65: Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

[1413] Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify fusion proteins which

bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

[1414] The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

[1415] For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

[1416] A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

[1417] For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to $2\text{-}5x10^6$ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to $1x10^6$ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

[1418] For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The fusion protein of the invention is added to the well, and a change in fluorescence is detected.

[1419] To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by an albumin fusion protein of the present invention or a molecule

induced by an albumin fusion protein of the present invention, which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 66: Assay Identifying Tyrosine Kinase Activity

[1420] The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

[1421] Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

[1422] Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether an albumin fusion protein of the present invention or a molecule induced by a fusion protein of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

[1423] Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in

growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

[1424] To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or a different concentrations of an albumin fusion protein of the invention, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN)) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

[1425] Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

[1426] Generally, the tyrosine kinase activity of an albumin fusion protein of the invention is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

[1427] The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5

mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

[1428] The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice. Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

[1429] Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 67: Assay Identifying Phosphorylation Activity

[1430] As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 66, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

[1431] Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above

described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

[1432] A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or varying concentrations of the fusion protein of the invention for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

[1433] After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by the fusion protein of the present invention or a molecule induced by an albumin fusion protein of the present invention.

Example 68: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

[1434] This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of fusion proteins of the inventon to stimulate proliferation of CD34+ cells.

[1435] It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of fusion proteins of the invention on hematopoietic activity of a wide range of progenitor cells, the assay contains a given fusion protein of the invention in the presence or absence of hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested fusion protein has a stimulatory effect on hematopoietic

progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given fusion protein might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

[1436] Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5 x 10^5 cells/ml. During this time, 100 µl of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with an albumin fusion protein of the invention in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 µl of prepared cytokines, varying concentrations of an albumin fusion protein of the invention, and 20 µl of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 µl. The plates are then placed in a 37°C/5% CO_2 incubator for five days.

[1437] Eighteen hours before the assay is harvested, 0.5 µCi/well of [3H] Thymidine is added in a 10 µl volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 µl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film A bar code 15 sticker is affixed to the first plate for counting. The sealed plates are then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

[1438] The studies described in this example test the activity of a given fusion protein to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of fusion porteins and polynucleotides of the invention (e.g., gene therapy) as well as agonists and antagonists thereof. The

ability of an albumin fusion protein of the invention to stimulate the proliferation of bone marrow CD34+ cells indicates that the albumin fusion protein and/or polynucleotides corresponding to the fusion protein are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 69: Assay for Extracellular Matrix Enhanced Cell Response (EMECR)

[1439] The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to evaluate the ability of fusion proteins of the invention to act on hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

[1440] Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5.\beta_1$ and $\alpha_4.\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and are responsible for stimulating stem cell self-renewal havea not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

[1441] Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of 0.2 $\mu g/ cm^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Albumin fusion proteins of the invention are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where volume of the administed composition containing the albumin fusion protein of the invention represents 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2, 7% O_2, and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine

incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

[1442] If a particular fusion protein of the present invention is found to be a stimulator of hematopoietic progenitors, the fusion protein and polynucleotides corresponding to the fusion protein may be useful for example, in the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above; and elsewhere herein. The fusion protein may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

[1443] Additionally, the albumin fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

[1444] Moreover, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 70: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

[1445] An albumin fusion protein of the invention is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the fusion protein on the proliferation of normal human dermal fibroblasts (NHDF) or aortic

smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNFa stimulation, in order to check for costimulatory or inhibitory activity.

[1446] Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 µl culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 µg/ml hEGF, 5mg/ml insulin, 1µg/ml hFGF, 50mg/ml gentamycin, 50 µg/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37 °C until day 2.

[1447] On day 2, serial dilutions and templates of an albumin fusion protein of the invention are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or an albumin fusion protein of the invention and incubate at 37 degrees C/5% CO_2 until day 5.

[1448] Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4 degrees C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

[1449] On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

[1450] On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

[1451] Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels.

[1452] Add 100 µl/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay were tabulated and averaged.

[1453] A positive result in this assay suggests AoSMC cell proliferation and that the albumin fusion protein may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of the fusion protein and polynucleotides encoding the albumin fusion protein. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, fusion proteins may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, fusion proteins showing antagonistic activity in this assay may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular agent (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion

fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, albumin fusion proteins that act as antagonists in this assay may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

Example 71: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

[1454] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[1455] Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing (containing an albumin fusion protein of the invention) and positive or negative controls are added to the plate in triplicate (in 10 μl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody).

Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μl of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 72: Alamar Blue Endothelial Cells Proliferation Assay

[1456] This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

[1457] Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37 degreesC overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of an albumin fusion protein

of the invention or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

[1458] Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form (i.e., stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity). The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 73: Detection of Inhibition of a Mixed Lymphocyte Reaction

[1459] This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by fusion proteins of the invention. Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by the albumin fusion proteins that inhibit MLR since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

[1460] Albumin fusion proteins of the invention found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease,

ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

[1461] Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM®, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x 10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x 10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of the fusion protein test material (50 µl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 µg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 µg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO_2, and 1 µC of [^{3}H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

[1462] Samples of the fusion protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

Example 74: Assays for Protease Activity

[1463] The following assay may be used to assess protease activity of an albumin fusion protein of the invention.

[1464] Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)). Samples are run on 10% polyacryamide/0.1% SDS gels containing 1% gelain orcasein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis apear as clear areas agains the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

[1465] Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mMNaPO$_4$,1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control.

[1466] Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983)).

Example 75: Identifying Serine Protease Substrate Specificity

[1467] Methods known in the art or described herein may be used to determine the substrate specificity of the albumin fusion proteins of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional scanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

Example 76: Ligand Binding Assays

[1468] The following assay may be used to assess ligand binding activity of an albumin fusion protein of the invention.

[1469] Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for an albumin fusion protein of the invention is radiolabeled to high specific activity (50-2000 Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards the fusion protein. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell polypeptide sources. For these assays, specific polypeptide binding is defined as total associated radioactivity minus the radioactivity measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

Example 77: Functional Assay in Xenopus Oocytes

[1470] Capped RNA transcripts from linearized plasmid templates encoding an albumin fusion protein of the invention is synthesized in vitro with RNA polymerases in accordance with standard procedures. In vitro transcripts are suspended in water at a final concentration of 0.2 mg/mi. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocytc) are injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response fusion protein and polypeptide agonist exposure. Recordings are made in Ca2+ free Barth's medium at room temperature. The Xenopus system can be used to screen known ligands and tissue/cell extracts for activating ligands.

Example 78: Microphysiometric Assays

[1471] Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the ability of an albumin fusion protein of the invention to activate secondary messengers that are coupled to an energy utilizing intracellular signaling pathway.

Example 79: Extract/Cell Supernatant Screening

[1472] A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the albumin fusion proteins of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify natural ligands for the Therapeutic protein portion and/or albumin protein portion of an albumin fusion protein of the invention. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand

is isolated and identified.

Example 80: ATP-binding assay

[1473] The following assay may be used to assess ATP-binding activity of fusion proteins of the invention.

[1474] ATP-binding activity of an albumin fusion protein of the invention may be detected using the ATP-binding assay described in U.S. Patent 5,858,719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to an albumin fusion protein of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of ABC transport protein are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (^{32}P-ATP) (5 mCi/μmol, ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the albumin fusion proteins of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenly-5'-imidodiphosphate provides a measure of ATP affinity to the fusion protein.

Example 81: Phosphorylation Assay

[1475] In order to assay for phosphorylation activity of an albumin fusion protein of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled ^{32}P-ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The fusion portein of the invention is incubated with the protein substrate, ^{32}P-ATP, and a kinase buffer. The ^{32}P incorporated into the substrate is then separated from free ^{32}P-ATP by electrophoresis, and the incorporated ^{32}P is counted and compared to a negative control. Radioactivity

counts above the negative control are indicative of phosphorylation activity of the fusion protein.

Example 82: Detection of Phosphorylation Activity (Activation) of an Albumin Fusion Protein of the Invention in the Presence of Polypeptide Ligands

[1476] Methods known in the art or described herein may be used to determine the phosphorylation activity of an albumin fusion protein of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

Example 83: Identification Of Signal Transduction Proteins That Interact With An albumin fusion protein Of The Present Invention

[1477] Albumin fusion proteins of the invention may serve as research tools for the identification, characterization and purification of signal transduction pathway proteins or receptor proteins. Briefly, a labeled fusion protein of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, an albumin fusion protein of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the albumin fusion protein. The protein complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 84: IL-6 Bioassay

[1478] A variety of assays are known in the art for testing the proliferative effects of an albumin fusion protein of the invention. For example, one such asssay is the IL-6 Bioassay as described by Marz *et al.* (*Proc. Natl. Acad. Sci., U.S.A., 95*:3251-56 (1998), which is herein incorporated by reference). After 68 hrs. at 37°C, the number of viable cells is measured by adding the tetrazolium salt thiazolyl blue (MTT) and incubating for a further 4 hrs. at 37°C. B9 cells are lysed by SDS and optical density is measured at 570 nm. Controls containing IL-6 (positive) and no cytokine (negative) are Briefly, IL-6

dependent B9 murine cells are washed three times in IL-6 free medium and plated at a concentration of 5,000 cells per well in 50 μl, and 50 μl of fusion protein of the invention is added. Enhanced proliferation in the test sample(s) (containing an albumin fusion protein of the invention) relative to the negative control is indicative of proliferative effects mediated by the fusion protein.

Example 85: Support of Chicken Embryo Neuron Survival

[1479] To test whether sympathetic neuronal cell viability is supported by an albumin fusion protein of the invention, the chicken embryo neuronal survival assay of Senaldi *et al* may be utilized (*Proc. Natl. Acad. Sci., U.S.A., 96*:11458-63 (1998), which is herein incorporated by reference). Briefly, motor and sympathetic neurons are isolated from chicken embryos, resuspended in L15 medium (with 10% FCS, glucose, sodium selenite, progesterone, conalbumin, putrescine, and insulin; Life Technologies, Rockville, MD.) and Dulbecco's modified Eagles medium [with 10% FCS, glutamine, penicillin, and 25 mM Hepes buffer (pH 7.2); Life Technologies, Rockville, MD.], respectively, and incubated at 37°C in 5% CO_2 in the presence of different concentrations of the purified fusion protein of the invention, as well as a negative control lacking any cytokine. After 3 days, neuron survival is determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mosmann, T., *J. Immunol. Methods, 65*:55-63 (1983)). Enhanced neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the albumin fusion protein to enhance the survival of neuronal cells.

Example 86: Assay for Phosphatase Activity

[1480] The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of an albumin fusion protein of the invention.

[1481] In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity of an albumin fusion protein of the invention may be measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [^{32}P]ATP.

Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from 32P-labeled MyBP.

Example 87: Interaction of Serine/Threonine Phosphatases with other Proteins

[1482] Fusion protein of the invention having serine/threonine phosphatase activity (e.g., as determined in Example 86) are useful, for example, as research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, a labeled fusion protein of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, an albumin fusion protein of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the fusion protein. The fusion protein -complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

Example 88: Assaying for Heparanase Activity

[1483] There a numerous assays known in the art that may be employed to assay for heparanase activity of an albumin fusion protein of the invention. In one example, heparanase activity of an albumin fusion protein of the invention, is assayed as described by Vlodavsky et al., (Vlodavsky et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media, intact cells (1×10^6 cells per 35-mm dish), cell culture supernatant, or purified fusion protein are incubated for 18 hrs at 37°C, pH 6.2-6.6, with ^{35}S-labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at $0.5 < K_{av} < 0.8$ (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of an albumin fusion protein of the invention in cleaving heparan sulfate.

Example 89: Immobilization of biomolecules

[1484] This example provides a method for the stabilization of an albumin fusion protein of the invention in non-host cell lipid bilayer constucts (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of fusion proteins of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to an albumin fusion protein of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of an albumin fusion protein of the invention in washed membranes is incubated with 20 mM NaIO4 and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl2, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

Example 90: Assays for Metalloproteinase Activity

[1485] Metalloproteinases are peptide hydrolases which use metal ions, such as Zn^{2+}, as the catalytic mechanism. Metalloproteinase activity of an albumin fusion protein of the present invention can be assayed according to methods known in the art. The following exemplary methods are provided:

Proteolysis of alpha-2-macroglobulin

[1486] To confirm protease activity, a purified fusion protein of the invention is mixed with the substrate alpha-2-macroglobulin (0.2 unit/ml; Boehringer Mannheim, Germany) in 1x assay buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 μM $ZnCl_2$ and 0.05% Brij-35) and incubated at 37°C for 1-5 days. Trypsin is used as positive control. Negative controls contain only alpha-2-macroglobulin in assay buffer. The samples are collected and boiled in SDS-PAGE sample buffer containing 5% 2-mercaptoethanol for 5-min, then loaded onto 8% SDS-polyacrylamide gel. After electrophoresis the proteins are visualized by silver staining. Proteolysis is evident by the appearance of lower molecular

weight bands as compared to the negative control.

Inhibition of alpha-2-macroglobulin proteolysis by inhibitors of metalloproteinases

[1487] Known metalloproteinase inhibitors (metal chelators (EDTA, EGTA, AND $HgCl_2$), peptide metalloproteinase inhibitors (TIMP-1 and TIMP–2), and commercial small molecule MMP inhibitors) may also be used to characterize the proteolytic activity of an albumin fusion protein of the invention. Three synthetic MMP inhibitors that may be used are: MMP inhibitor I, [IC_{50} = 1.0 μM against MMP-1 and MMP–8; IC_{50} = 30 μM against MMP-9; IC_{50} = 150 μM against MMP-3]; MMP-3 (stromelysin-1) inhibitor I [IC_{50} = 5 μM against MMP-3], and MMP-3 inhibitor II [K_i = 130 nM against MMP-3]; inhibitors available through Calbiochem, catalog # 444250, 444218, and 444225, respectively). Briefly, different concentrations of the small molecule MMP inhibitors are mixed with a purified fusion protein of the invention (50μg/ml) in 22.9 μl of 1x HEPES buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 μM $ZnCl_2$ and 0.05%Brij-35) and incubated at room temperature (24 °C) for 2-hr, then 7.1 μl of substrate alpha-2-macroglobulin (0.2 unit/ml) is added and incubated at 37°C for 20-hr. The reactions are stopped by adding 4x sample buffer and boiled immediately for 5 minutes. After SDS-PAGE, the protein bands are visualized by silver stain.

Synthetic Fluorogenic Peptide Substrates Cleavage Assay

[1488] The substrate specificity for fusion proteins of the invention with demonstrated metalloproteinase activity may be determined using techniques knonw in the art, such as using synthetic fluorogenic peptide substrates (purchased from BACHEM Bioscience Inc). Test substrates include, M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of tumor necrosis factor-α (TNF-α) converting enzyme (TACE). These substrastes are preferably prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are 50-500 μM. Fluorescent assays are performed by using a Perkin Elmer LS 50B luminescence spectrometer equipped with a constant temperature water bath. The excitation λ is 328 nm and the emission λ is 393 nm. Briefly, the assay is carried out by incubating 176 μl 1x HEPES buffer (0.2 M NaCl, 10 mM $CaCl_2$, 0.05% Brij-35 and 50 mM HEPES, pH 7.5) with 4 μl of substrate solution (50

μM) at 25 °C for 15 minutes, and then adding 20 μl of a purified fusion protein of the invention into the assay cuvett. The final concentration of substrate is 1 μM. Initial hydrolysis rates are monitored for 30-min.

Example 91: Identification And Cloning Of VH And VL Domains

[1489] One method to identify and clone VH and VL domains from cell lines expressing a particular antibody is to perform PCR with VH and VL specific primers on cDNA made from the antibody expressing cell lines. Briefly, RNA is isolated from the cell lines and used as a template for RT-PCR designed to amplify the VH and VL domains of the antibodies expressed by the EBV cell lines. Cells may be lysed in the TRIzol® reagent (Life Technologies, Rockville. MD) and extracted with one fifth volume of chloroform. After addition of chloroform, the solution is allowed to incubate at room temperature for 10 minutes, and the centrifuged at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. The supernatant is collected and RNA is precipitated using an equal volume of isopropanol. Precipitated RNA is pelleted by centrifuging at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. Following centrifugation, the supernatant is discarded and washed with 75% ethanol. Following washing, the RNA is centrifuged again at 800 rpm for 5 minutes at 4°C. The supernatant is discarded and the pellet allowed to air dry. RNA is the dissolved in DEPC water and heated to 60°C for 10 minutes. Quantities of RNA can determined using optical density measurements.

[1490] cDNA may be synthesized, according to methods well-known in the art, from 1.5-2.5 micrograms of RNA using reverse transcriptase and random hexamer primers. cDNA is then used as a template for PCR amplification of VH and VL domains. Primers used to amplify VH and VL genes are shown in Table 6. Typically a PCR reaction makes use of a single 5' primer and a single 3' primer. Sometimes, when the amount of available RNA template is limiting, or for greater efficiency, groups of 5' and/or 3' primers may be used. For example, sometimes all five VH-5' primers and all JH3' primers are used in a single PCR reaction. The PCR reaction is carried out in a 50 microliter volume containing 1X PCR buffer, 2mM of each dNTP, 0.7 units of High Fidelity Taq polymerse, 5' primer mix, 3' primer mix and 7.5 microliters of cDNA. The 5' and 3' primer mix of both VH and VL can be made by pooling together 22 pmole and 28 pmole, respectively, of each of the individual primers. PCR conditions are: 96°C for 5 minutes; followed by 25 cycles of

94°C for 1 minute, 50°C for 1 minute, and 72°C for 1 minute; followed by an extension cycle of 72°C for 10 minutes. After the reaction is completed, sample tubes are stored 4°C.

Table 6: Primer Sequences Used to Amplify VH and VL domains.

Primer name	SEQ ID NO	Primer Sequence (5'-3')
VH Primers		
Hu VH1-5'	342	CAGGTGCAGCTGGTGCAGTCTGG
Hu VH2-5'	343	CAGGTCAACTTAAGGGAGTCTGG
Hu VH3-5'	344	GAGGTGCAGCTGGTGGAGTCTGG
Hu VH4-5'	345	CAGGTGCAGCTGCAGGAGTCGGG
Hu VH5-5'	346	GAGGTGCAGCTGTTGCAGTCTGC
Hu VH6-5'	347	CAGGTACAGCTGCAGCAGTCAGG
Hu JH1,2-5'	348	TGAGGAGACGGTGACCAGGGTGCC
Hu JH3-5'	349	TGAAGAGACGGTGACCATTGTCCC
Hu JH4,5-5'	350	TGAGGAGACGGTGACCAGGGTTCC
Hu JH6-5'	351	TGAGGAGACGGTGACCGTGGTCCC
VL Primers		
Hu Vkappa1-5'	352	GACATCCAGATGACCCAGTCTCC
Hu Vkappa2a-5'	353	GATGTTGTGATGACTCAGTCTCC
Hu Vkappa2b-5'	354	GATATTGTGATGACTCAGTCTCC
Hu Vkappa3-5'	355	GAAATTGTGTTGACGCAGTCTCC
Hu Vkappa4-5'	356	GACATCGTGATGACCCAGTCTCC
Hu Vkappa5-5'	357	GAAACGACACTCACGCAGTCTCC
Hu Vkappa6-5'	358	GAAATTGTGCTGACTCAGTCTCC
Hu Vlambda1-5'	359	CAGTCTGTGTTGACGCAGCCGCC
Hu Vlambda2-5'	360	CAGTCTGCCCTGACTCAGCCTGC
Hu Vlambda3-5'	361	TCCTATGTGCTGACTCAGCCACC
Hu Vlambda3b-5'	362	TCTTCTGAGCTGACTCAGGACCC
Hu Vlambda4-5'	363	CACGTTATACTGACTCAACCGCC
Hu Vlambda5-5'	364	CAGGCTGTGCTCACTCAGCCGTC
Hu Vlambda6-5'	365	AATTTTATGCTGACTCAGCCCCA
Hu Jkappa1-3'	366	ACGTTTGATTTCCACCTTGGTCCC
Hu Jkappa2-3'	367	ACGTTTGATCTCCAGCTTGGTCCC
Hu Jkappa3-3'	368	ACGTTTGATATCCACTTTGGTCCC
Hu Jkappa4-3'	369	ACGTTTGATCTCCACCTTGGTCCC
Hu Jkappa5-3'	370	ACGTTTAATCTCCAGTCGTGTCCC
Hu Jlambda1-3'	371	CAGTCTGTGTTGACGCAGCCGCC
Hu Jlambda2-3'	372	CAGTCTGCCCTGACTCAGCCTGC
Hu Jlambda3--3'	373	TCCTATGTGCTGACTCAGCCACC
Hu Jlambda3b-3'	374	TCTTCTGAGCTGACTCAGGACCC
Hu Jlambda4-3'	375	CACGTTATACTGACTCAACCGCC
Hu Jlambda5-3'	376	CAGGCTGTGCTCACTCAGCCGTC
Hu Jlambda6-3'	377	AATTTTATGCTGACTCAGCCCCA

[1491] PCR samples are then electrophoresed on a 1.3% agarose gel. DNA bands of the expected sizes (~506 base pairs for VH domains, and 344 base pairs for VL domains) can be cut out of the gel and purified using methods well known in the art. Purified PCR products can be ligated into a PCR cloning vector (TA vector from Invitrogen Inc., Carlsbad, CA). Individual cloned PCR products can be isolated after transfection of E. coli and blue/white color selection. Cloned PCR products may then be sequenced using methods commonly known in the art.

[1492] The PCR bands containing the VH domain and the VL domains can also be used to create full-length Ig expression vectors. VH and VL domains can be cloned into vectors containing the nucleotide sequences of a heavy (e.g., human IgG1 or human IgG4) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods using polynucleotides encoding VH and VL antibody domain to generate expression vectors that encode complete antibody molecules are well known within the art.

EXAMPLE 92: Construct ID 2249, IFNa2-HSA, Generation.

[1493] Construct ID 2249, pSAC35:IFNa2.HSA, comprises DNA encoding an IFNa2 albumin fusion protein which has the HSA chimeric leader sequence, followed by the mature form of IFNa2 protein, i.e., C1-E165, fused to the amino-terminus of the mature form of HSA in the yeast *S. cerevisiae* expression vector pSAC35.

Cloning of IFNa2 cDNA

[1494] The polynucleotide encoding IFNa2 was PCR amplified using primers IFNa2-1 and IFNa2-2, described below. The PCR amplimer was cut with *Sal I/Cla* I, and ligated into *Xho I/Cla* I cut pScCHSA. Construct ID #2249 encodes an albumin fusion protein containing the chimeric leader sequence of HSA, the mature form of IFNa2, followed by the mature HSA protein.

[1495] Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the mature form of IFNa2, IFNa2-1 and IFNa2-2, were synthesized:

IFNa2-1: 5'-CGCGCGCGTCGACAAAAGATGTGATCTGCCTCAAACCCACA-3' (SEQ ID NO:838)

IFNa2-2: 5'-GCGCGCATCGATGAGCAACCTCACTCTTGTGTGCATCTTCCTTAC TTCTTAAACTTTCT-3' (SEQ ID NO:839)

[1496] The IFNa2-1 primer incorporates a *Sal* I cloning site (shown underlined), nucleotides encoding the last three amino acid residues of the chimeric HSA leader sequence, as well as 22 nucleotides (shown in bold) encoding the first 7 amino acid residues of the mature form of IFNa2. In IFNa2-2, the *Cla* I site (shown underlined) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein and the last 22 nucleotides (shown in bold) are the reverse complement of DNA encoding the last 7 amino acid residues of IFNa2 (see Example 2). A PCR amplimer of IFNa2-HSA was generated using these primers, purified, digested with *Sal* I and *Cla* I restriction enzymes, and cloned into the *Xho* I and *Cla* I sites of the pScCHSA vector. After the sequence was confirmed, the expression cassette encoding this IFNa2 albumin fusion protein was subcloned into *Not* I digested pSAC35.

[1497] Further, analysis of the N-terminus of the expressed albumin fusion protein by amino acid sequencing can confirm the presence of the expected IFNa2 sequence (see below).

[1498] Other IFNa2 albumin fusion proteins using different leader sequences have been constructed by methods known in the art (see Example 2). Examples of the various leader sequences include, but are not limited to, invertase "INV" (constructs 2343 and 2410) and mating alpha factor "MAF" (construct 2366). These IFNa2 albumin fusion proteins can be subcloned into mammalian expression vectors such as pC4 (constructs 2382) and pEE12.1 as described previously (see Example 5). IFNa2 albumin fusion proteins with the therapeutic portion fused C-terminus to HSA can also be constructed (construct 2381).

[1499] IFNa2 albumin fusion proteins of the invention preferably comprise the mature form of HSA , i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the mature form of IFNa2, i.e., Cys-1 to Glu-165. In one embodiment of the invention, IFNa2 albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is

removed, and the mature IFNa2 albumin fusion protein is secreted directly into the culture medium. IFNa2 albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, IFNa2 albumin fusion proteins of the invention comprise the native IFNa2. In further preferred embodiments, the IFNa2 albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

Expression and Purification of Construct ID 2249.

Expression in yeast S. cerevisiae.

[1500] Transformation of construct 2249 into yeast *S. cerevisiae* strain BXP10 was carried out by methods known in the art (see Example 3). Cells can be collected at stationary phase after 72 hours of growth. Supernatants are collected by clarifying cells at 3000g for 10 min. Expression levels are examined by immunoblot detection with anti-HSA serum (Kent Laboratories) or as the primary antibody. The IFNa2 albumin fusion protein of approximate molecular weight of 88.5 kDa can be obtained.

Purification from yeast S. cerevisiae cell supernatant.

[1501] The cell supernatant containing IFNa2 albumin fusion protein expressed from construct ID #2249 in yeast *S. cerevisiae* cells can be purified either small scale over a Dyax peptide affinity column (see Example 4) or large scale by following 5 steps: diafiltration, anion exchange chromatography using DEAE-Sepharose Fast Flow column, hydrophobic interaction chromatography (HIC) using Butyl 650S column, cation exchange chromatography using an SP-Sepharose Fast Flow column or a Blue-Sepharose chromatography, and high performance chromatography using Q-sepharose high performance column chromatography (see Example 4). The IFNa2 albumin fusion protein may elute from the DEAE-Sepharose Fast Flow column with 100 – 250 mM NaCl, from the SP-Sepharose Fast Flow column with 150 – 250 mM NaCl, and from the Q-Sepharose High Performance column at 5 – 7.5 mS/cm. N-terminal sequencing should yield the sequence CDLPQ (SEQ ID NO:849) which corresponds to the mature form of IFNa2.

The activity of IFNa2 can be assayed using an in vitro ISRE-SEAP assay.

Method

[1502] The IFNa2 albumin fusion protein encoded by construct ID # 2249 can be tested for activity in the ISRE-SEAP assay as previously described in Example 19. Briefly, conditioned yeast supernatants were tested at a 1:1000 dilution for their ability to direct ISRE signal transduction on the ISRE-SEAP/293F reporter cell-line. The ISRE-SEAP/293F reporter cells were plated at 3 x 10^4 cell/well in 96-well, poly-D-lysine coated, plates, one day prior to treatment. The reporter cells were then incubated for 18 or 24 hours prior to removing 40 µL for use in the SEAP Reporter Gene Chemiluminescent Assay (Roche catalog # 1779842). Recombinant human Interferon beta, "rhIFNb" (Biogen), was used as a positive control.

Result

[1503] The purified preparation of IFNa2-HSA demonstrated a relatively linear increase in the ISRE-SEAP assay over concentrations ranging from 10^{-1} to 10^{1} ng/mL or 10^{-10} to 10^{-8} ng/mL (see Figure 9).

In vivo induction of OAS by Interferon alpha fusion encoded by construct ID 2249.

Method

[1504] The OAS enzyme, 2'-5'- OligoAdenylate Synthetase, is activated at the transcriptional level by interferon in response to antiviral infection. The effect of interferon constructs can be measured by obtaining blood samples from treated monkeys and analyzing these samples for transcriptional activation of two OAS mRNA, p41 and p69. A volume of 0.5 mL of whole blood was obtained from 4 animals per group at 7 different time points, day 0, day 1, day 2, day 4, day 8, day 10, and day 14 per animal. The various groups include vehicle control, intravenous injection of 30 µg/kg HSA-IFN on day 1, subcutaneous injection of 30 µg/kg of HSA-IFN on day 1, subcutaneous injection of 300 µg/kg of HSA-IFN on day 1, and subcutaneous injection of 40 µg/kg of Interferon alpha (Schering-Plough) as a positive control on days 1, 3, and 5. The levels of the p41 and the p69 mRNA transcripts were determined by real-time quantitative PCR (Taqman) using probes specific for p41-OAS and p69-OAS. OAS mRNA levels were quantitated relative

to 18S ribosomal RNA endogenous control. The albumin fusion encoded by construct 2249 can be subjected to similar experimentation.

Results

[1505] A significant increase in mRNA transcript levels for both p41 and p69 OAS was observed in HSA-interferon treated monkeys in contrast to IFNa treated monkeys (see Figure 10 for p41 data). The effect lasted nearly 10 days.

EXAMPLE 93: Indications for IFNa2 Albumin Fusion Proteins

[1506] IFN alpha albumin fusion protein (including, but not limited to, those encoded by constructs 2249, 2343, 2410, 2366, 2382, and 2381) can be used to treat, prevent, ameliorate, and/or detect multiple sclerosis. Other indications include, but are not limited to, Hepatitis C, oncology uses, cancer, hepatitis, human papilloma virus, fibromyalgia, Sjogren's syndrome, hairy cell leukemia, chronic myelogeonus leukemia, AIDS-related Kaposi's sarcoma, chronic hepatitis B, malignant melanoma, non-Hodgkin's lymphoma, external condylomata acuminata, HIV infection, small cell lung cancer, hematological malignancies, herpes simplex virus infections, multiple sclerosis, viral hemorrhagic fevers, solid tumors, renal cancer, bone marrow disorders, bone disorders, bladder cancer, gastric cancer, hepatitis D, multiple myeloma, type I diabetes mellitus, viral infections, cutaneous T-cell lymphoma, cervical dysplasia, chronic fatigue syndrome, and renal cancer.

[1507] Preferably, the IFNα-albumin fusion protein or IFN hybrid fusion protein is administered in combination with a CCR5 antagonist, further in association with at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with an anti-HIV drug therapy, e.g., HAART, for preparation of a medicament for the treatment of HIV-1 infections, HCV, or HIV-1 and HCV co-infections in treatment-naïve as well as treatment-experienced adult and pediatric patients.

Example 94: Preparation of HA-IFN fusion proteins (such as IFNα).

[1508] The cDNA for the interferon of interest such as IFNα can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for interferons, such as IFNα are known and available, for instance, in U.S. Patents 5,326,859 and 4,588,585, in EP 32 134, as well as in public

databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used to clone the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus of the HA sequence, with or without the use of a spacer sequence. The IFNα (or other interferon) cDNA is cloned into a vector such as pPPC0005 (Figure 3), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

Maximum protein recovery from vials

[1509] The albumin fusion proteins of the invention have a high degree of stability even when they are packaged at low concentrations. In addition, in spite of the low protein concentration, good fusion-protein recovery is observed even when the aqueous solution includes no other protein added to minimize binding to the vial walls. The recovery of vial-stored HA-IFN solutions was compared with a stock solution. 6 or 30 μg/ml HA-IFN solutions were placed in vials and stored at 4°C. After 48 or 72 hrs a volume originally equivalent to 10 ng of sample was removed and measured in an IFN sandwich ELISA. The estimated values were compared to that of a high concentration stock solution. As shown, there is essentially no loss of the sample in these vials, indicating that addition of exogenous material such as albumin is not necessary to prevent sample loss to the wall of the vials

In vivo stability and bioavailability of HA-α-IFN fusions

[1510] To determine the in vivo stability and bioavailability of a HA-α-IFN fusion molecule, the purified fusion molecule (from yeast) was administered to monkeys. Pharmaceutical compositions formulated from HA-α-IFN fusions may account for the extended serum half-life and bioavailability. Accordingly, pharmaceutical compositions

may be formulated to contain lower dosages of alpha-interferon activity compared to the native alpha-interferon molecule.

[1511] Pharmaceutical compositions containing HA-α-IFN fusions may be used to treat or prevent disease in patients with any disease or disease state that can be modulated by the administration of α-IFN. Such diseases include, but are not limited to, hairy cell leukemia, Kaposi's sarcoma, genital and anal warts, chronic hepatitis B, chronic non-A, non-B hepatitis, in particular hepatitis C, hepatitis D, chronic myelogenous leukemia, renal cell carcinoma, bladder carcinoma, ovarian and cervical carcinoma, skin cancers, recurrent respirator papillomatosis, non-Hodgkin's and cutaneous T-cell lymphomas, melanoma, multiple myeloma , AIDS, multiple sclerosis, gliobastoma, etc. (see Interferon Alpha, In: AHFS Drug Information, 1997.

[1512] Accordingly, the invention includes pharmaceutical compositions containing a HA-α-IFN fusion protein, polypeptide or peptide formulated with the proper dosage for human administration. The invention also includes methods of treating patients in need of such treatment comprising at least the step of administering a pharmaceutical composition containing at least one HA-α-IFN fusion protein, polypeptide or peptide.

Bifunctional HA-α-IFN fusions

[1513] A HA-α-IFN expression vector may be modified to include an insertion for the expression of bifunctional HA-α-IFN fusion proteins. For instance, the cDNA for a second protein of interest may be inserted in frame downstream of the "rHA-IFN" sequence after the double stop codon has been removed or shifted downstream of the coding sequence.

[1514] In one version of a bifunctional HA-α-IFN fusion protein, an antibody or fragment against B-lymphocyte stimulator protein (GenBank Acc 4455139) or polypeptide may be fused to one end of the HA component of the fusion molecule. This bifunctional protein is useful for modulating any immune response generated by the α-IFN component of the fusion.

Example 95: Expression of an Albumin Fusion Protein in Mammalian Cells.

[1515] The albumin fusion proteins of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and

signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[1516] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as, pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, but are not limited to, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[1517] Alternatively, the albumin fusion protein can be expressed in stable cell lines containing the polynucleotide encoding the albumin fusion protein integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

[1518] The transfected polynucleotide encoding the fusion protein can also be amplified to express large amounts of the encoded fusion protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin et al., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page et al., Biotechnology 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

[1519] Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-

enhancer (Boshart et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

[1520] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

[1521] A polynucleotide encoding an albumin fusion protein of the present invention is generated using techniques known in the art and this polynucleotide is amplified using PCR technology known in the art. If a naturally occurring signal sequence is used to produce the fusion protein of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

[1522] The amplified fragment encoding the fusion protein of the invention is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[1523] The amplified fragment encoding the albumin fusion protein of the invention is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

[1524] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM

supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired fusion protein is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

EXAMPLE 96: Construct ID 2876, HSA-IFNα hybrid

[1525] Construct ID 2876, pSAC35:HSA.IFNαA(C1-Q91)/D(L93-E166) R23K,A113V comprises DNA encoding an IFNα hybrid albumin fusion protein which has mature HSA fused downstream of the HSA/kex2 leader sequence and upstream of an IFNα A/D hybrid amino acid sequence, in the yeast S. cerevisiae expression vector pSAC35. Regarding the composition of the hybrid IFN, the first 91 amino acids are from the subtype IFNα2 (also called IFNαA) and the remaining 75 aa are from IFNα1 (IFNαD). We incorporated two point mutations (R23K, A113V). The fusion was generated by PCR and fused downstream of HSA within the yeast expression vector pSAC35.

Results

CID 2876 Expression and Purification

[1526] The yeast strain BXP-10 was transformed with pSAC35:CID 2876 and a transformant selected for fermentation. A 5-liter fermentation was performed and analysis of supernatant demonstrated high expression (approximately 500 mg/l). A small proportion of the supernatant was processed to pilot purification. Approximately 1 mg of CID 2876 protein (greater than 95% pure based on N-terminal sequence) was obtained following a purification through Blue-sepharose, followed by gel filtration, followed by Q-anion exchange. The remaining fermentation starting material is available for further purification if needed.

ISRE Activity

[1527] All type I IFNs mediate their activities through engagement of a common IFN receptor complex and activation of the ISRE signal transduction pathway. Activation of gene transcription through this pathway leads to the cellular responses associated with IFNs including anti-proliferation, antiviral and immune modulation. Using a reporter based strategy, the ability of CID 2876 to activate the ISRE signal transduction pathway was determined. CID 2876 was found to be a potent activator of the ISRE pathway, demonstrating an EC_{50} of 2.7 ng/ml (data not shown). This compares favorably with the potency of CID 3165 in this assay system.

Anti-viral activity

[1528] A hallmark activity of IFNs is their ability to mediate cellular protection against viral infection. While most human type I IFNs display antiviral activity in a species restricted manner, the hybrid IFN employed in this study has been demonstrated to be active on murine cells. Thus the antiviral activity of CID 2876 was evaluated on the murine cell line L929 infected with EMCV. Results indicate that CID 2876 does demonstrate antiviral activity in a cross species manner (data not shown).

[1529] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[1530] The entire disclosure of each document cited (including patents, patent applications, patent publications, journal articles, abstracts, laboratory manuals, books, or other disclosures) as well as information available through Identifiers specific to databases such as GenBank, GeneSeq, or the CAS Registry, referred to in this application are herein incorporated by reference in their entirety.

[1531] Furthermore, the specification and sequence listing of each of the following U.S. applications are herein incorporated by reference in their entirety: U.S. Application No. 60/341,811, filed December 21, 2001; U.S. Application No. 60/360,000, filed February 28, 2002; U.S. Application No. 60/378,950, filed May 10, 2002; U.S. Application No. 60/398,008, filed July 24, 2002; U.S. Application No. 60/411,355, filed September 18, 2002; U.S. Application No. 60/414,984, filed October 2, 2002; U.S. Application No. 60/417,611, filed October 11, 2002; U.S. Application No. 60/420,246,

filed October 23, 2002; U.S. Application No. 60/423,623, filed November 5, 2002; U.S. Application No. 60/350,358, filed January 24, 2002; U.S. Application No. 60/359,370, filed February 26, 2002; U.S. Application No. 60/367,500, filed March 27, 2002; U.S. Application No. 60/402,131, filed August 9, 2002; U.S. Application No. 60/402,708, filed August 13, 2002; and U.S. Application No. 60/370,227, filed April 8, 2002. Furthermore, the specification and the sequence listing of U.S. Application, Human Genome Sciences, Inc., attorney docket number PF564PCT, filed concurrently herewith on December 23, 2002, is hereby incorporated by reference in its entirety.

Applicant's File Reference Number: PF574PCT	International Application Number: Unassigned

INDICATIONS RELATING TO DEPOSITED BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited biological material referred to on pages 67 and 68 in Table 3 of the description.

B. IDENTIFICATION OF DEPOSIT: Further deposits are identified on an additional sheet: ☐

Name of Depository: **American Type Culture Collection**
Address of Depository: **10801 University Boulevard**
Manassas, Virginia 20110-2209
United States of America

	Accession Number	Date of Deposit		Accession Number	Date of Deposit
1	PTA-3916	07-Dec-2001	2	PTA-3917	07-Dec-2001
3	PTA-3918	07-Dec-2001	4	PTA-3764	04-Oct-2001
5	PTA-3941	19-Dec-2001	6	PTA-3763	04-Oct-2001
7	PTA-3940	19-Dec-2001	8	PTA-3942	19-Dec-2001
9	PTA-3939	19-Dec-2001	10	PTA-3943	19-Dec-2001
11	PTA-4671	16-Sep-2002	12	PTA-4670	16-Sep-2002

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What is claimed:

1. An albumin fusion protein comprising a member selected from the group consisting of:

(a) a Therapeutic protein:X and albumin comprising the amino acid sequence of SEQ ID NO:327;

(b) a Therapeutic protein:X and a fragment or a variant of the amino acid sequence of SEQ ID NO:327, wherein said fragment or variant has albumin activity;

(c) a Therapeutic protein:X and a fragment or a variant of the amino acid sequence of SEQ ID NO:327, wherein said fragment or variant has albumin activity, and further wherein said albumin activity is the ability to prolong the shelf life of the Therapeutic protein:X compared to the shelf-life of the Therapeutic protein:X in an unfused state;

(d) a Therapeutic protein:X and a fragment or a variant of the amino acid sequence of SEQ ID NO:327, wherein said fragment or variant has albumin activity, and further wherein the fragment or variant comprises the amino acid sequence of amino acids 1-387 of SEQ ID NO:327;

(e) a fragment or variant of a Therapeutic protein:X and albumin comprising the amino acid sequence of SEQ ID NO:327, wherein said fragment or variant has a biological activity of the Therapeutic protein:X;

(f) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), wherein the Therapeutic protein:X, or fragment or variant thereof, is fused to the N-terminus of albumin, or the N-terminus of the fragment or variant of albumin;

(g) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), wherein the Therapeutic protein:X, or fragment or variant thereof, is fused to the C-terminus of albumin, or the C-terminus of the fragment or variant of albumin;

(h) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), wherein the Therapeutic protein:X, or fragment or variant thereof, is fused to the N- terminus and C-terminus of albumin, or the N-terminus and the C-terminus of the fragment or variant of albumin;

(i) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (e), which comprises a first Therapeutic protein:X, or fragment or variant thereof, and a second Therapeutic protein:X, or fragment or variant thereof, wherein said first Therapeutic protein:X, or fragment or variant thereof, is different from said second Therapeutic protein:X, or fragment or variant thereof;

(j) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (i), wherein the Therapeutic protein:X, or fragment or variant thereof, is separated from the albumin or the fragment or variant of albumin by a linker; and

(k) a Therapeutic protein:X, or fragment or variant thereof, and albumin, or fragment or variant thereof, of (a) to (j), wherein the albumin fusion protein has the following formula:

R1-L-R2; R2-L-R1; or R1-L-R2-L-R1,

and further wherein R1 is Therapeutic protein:X, or fragment or variant thereof, L is a peptide linker, and R2 is albumin comprising the amino acid sequence of SEQ ID NO:327 or a fragment or variant of albumin.

2. The albumin fusion protein of claim 1, wherein the shelf-life of the albumin fusion protein is greater than the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

3. The albumin fusion protein of claim 1, wherein the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin, or fragment or variant thereof, is greater than the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

4. The albumin fusion protein of claim 1, wherein the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin, or fragment or variant thereof, is greater than the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

5. An albumin fusion protein comprising a Therapeutic protein:X, or fragment or

variant thereof, inserted into an albumin, or fragment or variant thereof, comprising the amino acid sequence of SEQ ID NO:327 or fragment or variant thereof.

6. An albumin fusion protein comprising a Therapeutic protein:X, or fragment or variant thereof, inserted into an albumin, or fragment or variant thereof, comprising an amino acid sequence selected from the group consisting of:

(a) amino acids 54 to 61 of SEQ ID NO:327;
(b) amino acids 76 to 89 of SEQ ID NO:327;
(c) amino acids 92 to100 of SEQ ID NO:327;
(d) amino acids 170 to 176 of SEQ ID NO:327;
(e) amino acids 247 to 252 of SEQ ID NO:327;
(f) amino acids 266 to 277 of SEQ ID NO:327;
(g) amino acids 280 to 288 of SEQ ID NO:327;
(h) amino acids 362 to 368 of SEQ ID NO:327;
(i) amino acids 439 to 447 of SEQ ID NO:327;
(j) amino acids 462 to 475 of SEQ ID NO:327;
(k) amino acids 478 to 486 of SEQ ID NO:327; and
(l) amino acids 560 to 566 of SEQ ID NO:327.

7. The albumin fusion protein of claim 5, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, as compared to the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

8. The albumin fusion protein of claim 6, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, as compared to the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

9. The albumin fusion protein of claim 5, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin as compared to the

in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

10. The albumin fusion protein of claim 6, wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin as compared to the in vitro biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

11. The albumin fusion protein of claim 5 wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin compared to the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

12. The albumin fusion protein of claim 6 wherein said albumin fusion protein comprises a portion of albumin sufficient to prolong the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, fused to albumin compared to the in vivo biological activity of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

13. The albumin fusion protein of any one of claims 1-12, which is non-glycosylated.

14. The albumin fusion protein of any one of claims 1-12, which is expressed in yeast.

15. The albumin fusion protein of claim 14, wherein the yeast is glycosylation deficient.

16. The albumin fusion protein of claim 14 wherein the yeast is glycosylation and protease deficient.

17. The albumin fusion protein of any one of claims 1-12, which is expressed by a mammalian cell.

18. The albumin fusion protein of any one of claims 1-12, wherein the albumin fusion protein is expressed by a mammalian cell in culture.

19. The albumin fusion protein of any one of claims 1-12, wherein the albumin fusion protein further comprises a secretion leader sequence.

20. A composition comprising the albumin fusion protein of any one of claims 1-12 and a pharmaceutically acceptable carrier.

21. A kit comprising the composition of claim 20.

22. A method of treating a disease or disorder in a patient, comprising the step of administering the albumin fusion protein of any one of claims 1-12.

23. A method of treating a metabolic/endocrine disorder in a patient, comprising administering the albumin fusion protein of any one of claims 1–12.

24. A method of treating diabetes or a condition associated with diabetes in a patient, comprising administering the albumin fusion protein of any one of claims 1-12.

25. The method of claim 24 wherein the diabetes is Type I diabetes.

26. The method of claim 24 wherein the diabetes is Type II diabetes.

27. The method of claim 24 wherein the condition is hyperglycemia.

28. The method of claim 24 wherein the condition is neural disorder.

29. The method of claim 28 wherein the disorder is neuropathy.

30. The method of claim 24 wherein the condition is retinopathy.

31. The method of claim 24 wherein the condition is a cardiovascular disorder.

32. The method of claim 31 wherein the condition is heart disease.

33. The method of claim 24 wherein the condition is renal disorder.

34. A method of treating obesity in a patient, comprising administering the albumin fusion protein of any one of claims 1-12.

35. A method of maintaining a basal glucose level in a patient, comprising administering the albumin fusion protein of any one of claims 1-12.

36 A method of losing weight in a patient, comprising administering the albumin fusion protein of any one of claims 1-12.

37. A method of extending the shelf life of Therapeutic protein:X, or fragment or variant thereof, comprising the step of fusing the Therapeutic protein:X, or fragment or variant thereof, to albumin, or fragment or variant thereof, sufficient to extend the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, compared to the shelf-life of the Therapeutic protein:X, or fragment or variant thereof, in an unfused state.

38. A nucleic acid molecule comprising a polynucleotide sequence encoding the albumin fusion protein of any one of claims 1-12.

39. A vector comprising the nucleic acid molecule of claim 38.

40. A host cell comprising the nucleic acid molecule of claim 39.

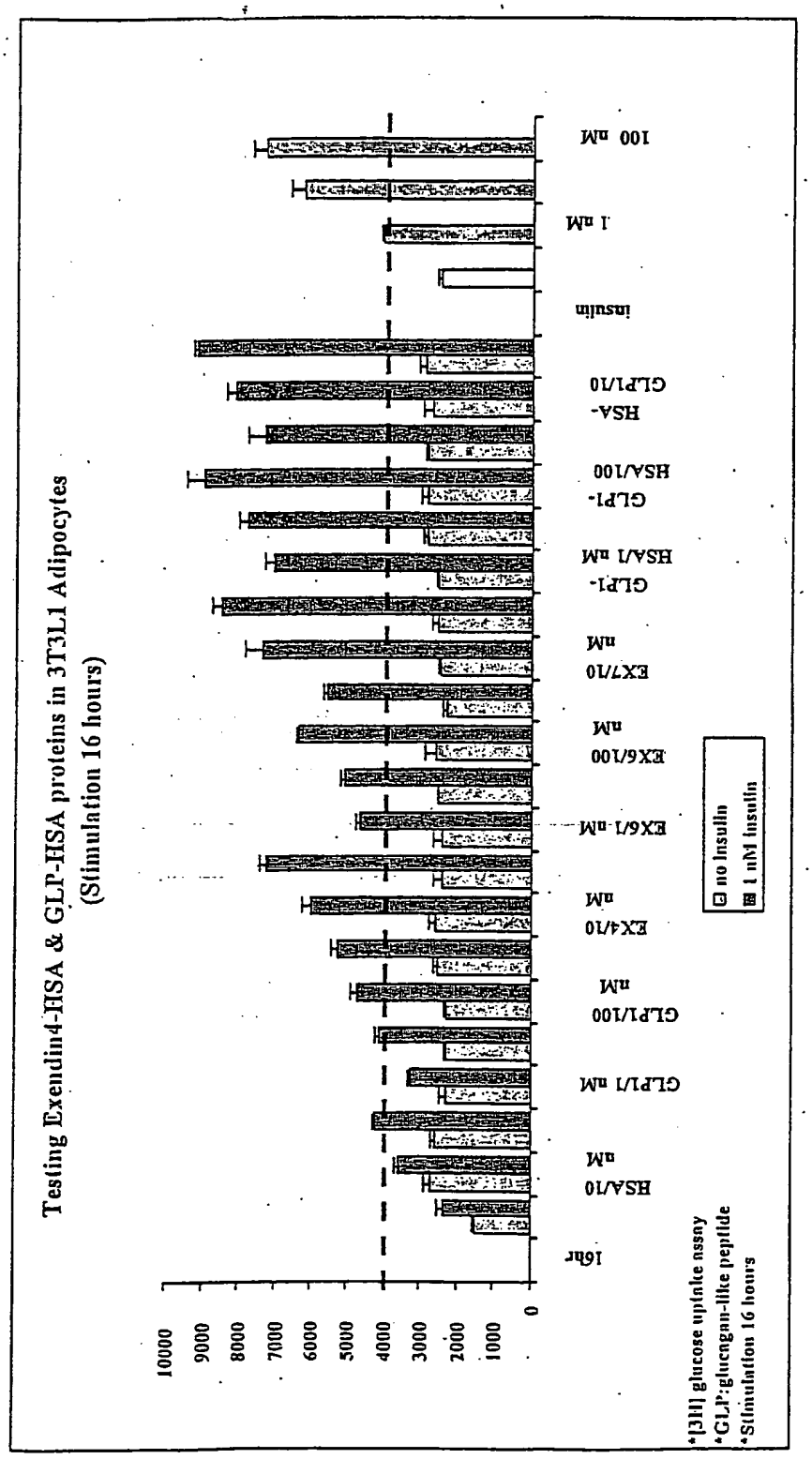
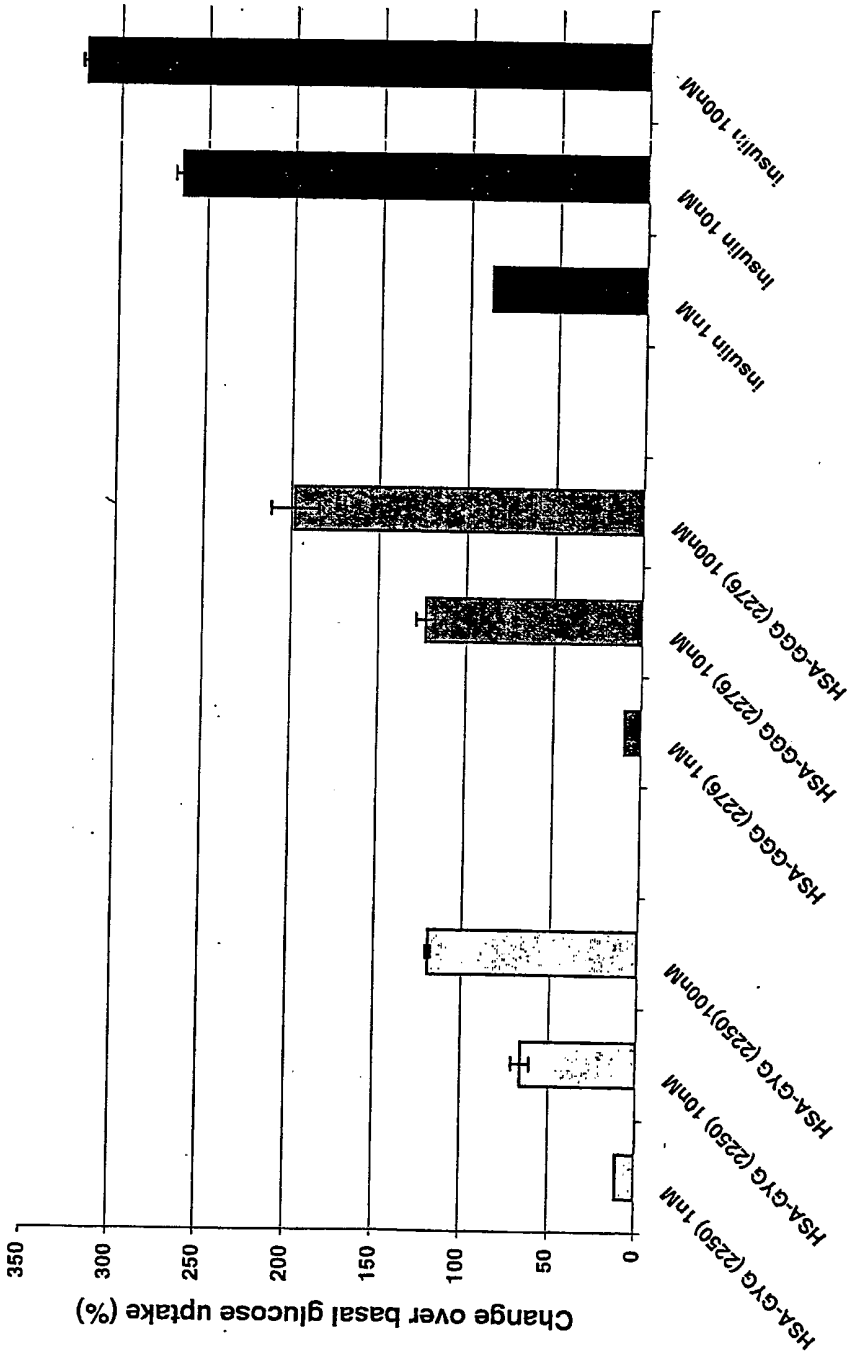
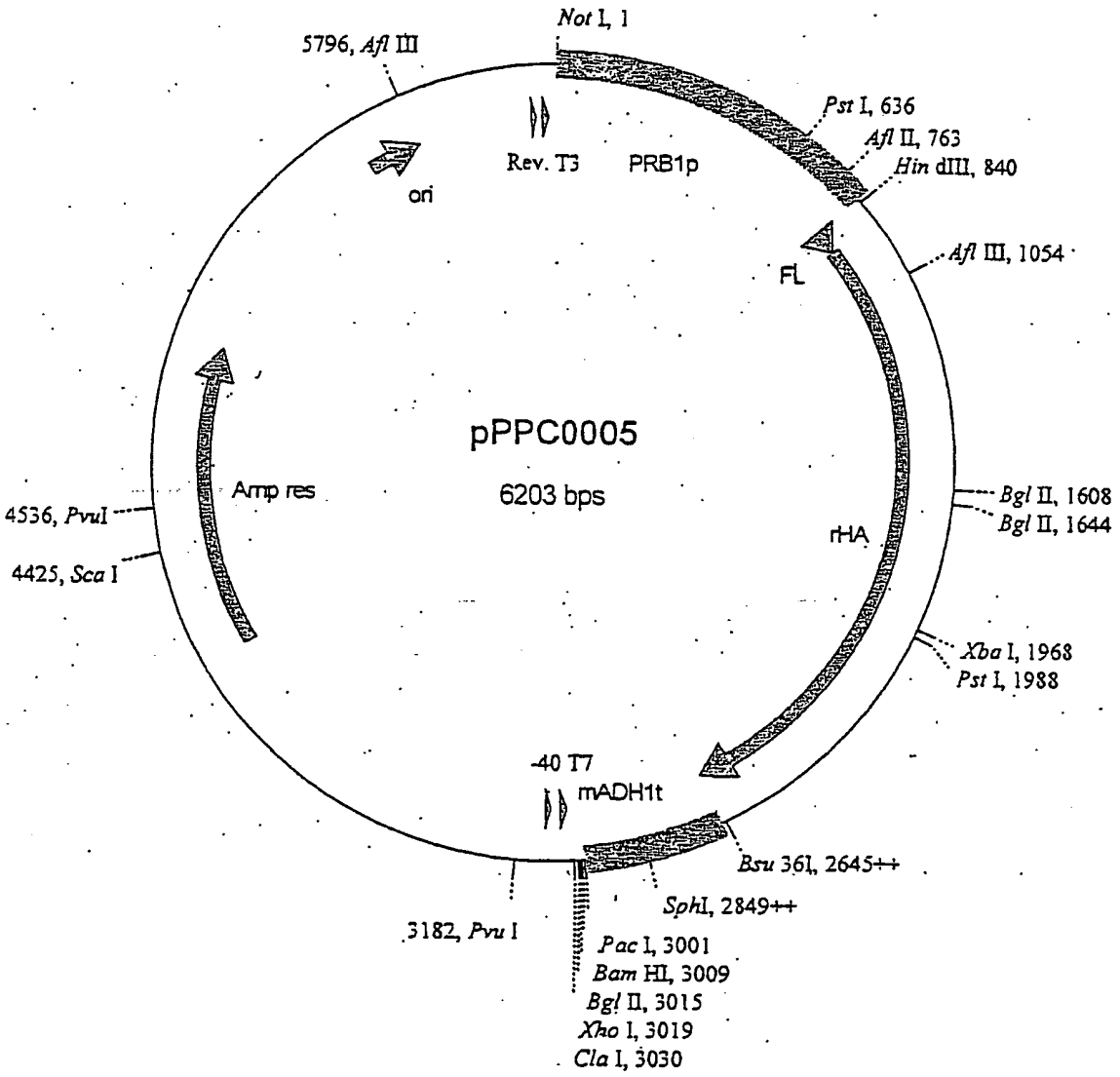

Testing Exendin4-HSA & GLP-HSA proteins in 3T3L1 Adipocytes
(Stimulation 16 hours)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
16hr
HSA/10 nM
GLP1/1 nM
GLP1/100 nM
EX4/10 nM
EX6/1 nM
EX6/100 nM
EX7/10 nM
GLP1-HSA/1 nM
GLP1-HSA/100
HSA-GLP1/10
insulin
1 nM
100 nM
no insulin
1 nM insulin
*[3H] glucose uptake assay
*GLP:glucagon-like peptide
*Stimulation 16 hours

Figure 1

FIGURE 2
Glucose uptake in 3T3 L1 adipocytes

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Afl II, 763
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Rev. T3
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FL
pPPC0005
6203 bps
Amp res
4536, PvuI
4425, Sca I
rHA
Bgl II, 1608
Bgl II, 1644
Xba I, 1968
Pst I, 1988
-40 T7
mADH1t
Bsu 36I, 2645++
SphI, 2849++
3182, Pvu I
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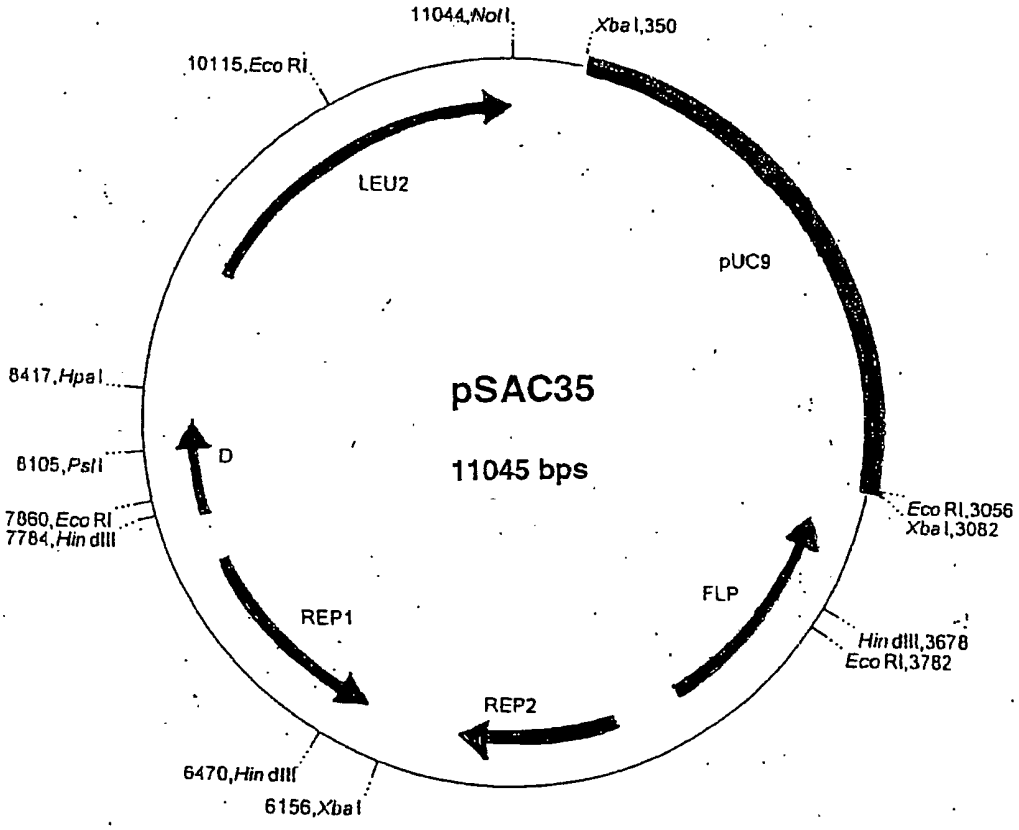
Bam HI, 3009
Bgl II, 3015
Xho I, 3019
Cla I, 3030

Figure 3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LEU2
pUC9
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8417,HpaI
8105,PstI
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7860,Eco RI
7784,Hin dIII
Eco RI,3056
Xba I,3082
FLP
REP1
Hin dIII,3678
Eco RI,3782
REP2
6470,Hin dIII
6156,XbaI

Figure 4

```
  1 GAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA GAA AAT TTC AAA 60
  1 D   A   H   K   S   E   V   A   H   R   F   K   D   L   G   E   E   N   F   K   20

 61 GCC TTG GTG TTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21 A   L   V   L   I   A   F   A   Q   Y   L   Q   Q   C   P   F   E   D   H   V   40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180
 41 K   L   V   N   E   V   T   E   F   A   K   T   C   V   A   D   E   S   A   E   60

181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61 N   C   D   K   S   L   H   T   L   F   G   D   K   L   C   T   V   A   T   L   80

241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81 R   E   T   Y   G   E   M   A   D   C   C   A   K   Q   E   P   E   R   N   E   100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360
101 C   F   L   Q   H   K   D   D   N   P   N   L   P   R   L   V   R   P   E   V   120

361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
121 D   V   M   C   T   A   F   H   D   N   E   E   T   F   L   K   K   Y   L   Y   140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
141 E   I   A   R   R   H   P   Y   F   Y   A   P   E   L   L   F   F   A   K   R   160
```

Figure 5A

```
481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC TGC CTG TTG CCA 540
161 Y   K   A   A   F   T   E   C   C   Q   A   A   D   K   A   A   C   L   L   P   180

541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT 600
181 K   L   D   E   L   R   D   E   G   K   A   S   S   A   K   Q   R   L   K   C   200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660
201 A   S   L   Q   K   F   G   E   R   A   F   K   A   W   A   V   A   R   L   S   220

661 CAG AGA TTT CCC AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
221 Q   R   F   P   K   A   E   F   A   E   V   S   K   L   V   T   D   L   T   K   240

721 GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GCT GAT GAC AGG GCG GAC CTT 780
241 V   H   T   E   C   C   H   G   D   L   L   E   C   A   D   D   R   A   D   L   260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 340
261 A   K   Y   I   C   E   N   Q   D   S   I   S   S   K   L   K   E   C   C   E   280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
281 K   P   L   L   E   K   S   H   C   I   A   E   V   E   N   D   E   M   P   A   300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
301 D   L   P   S   L   A   A   D   F   V   E   S   K   D   V   C   K   N   Y   A   320
```

Figure 5B

```
 961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020
 321 E   A   K   D   V   F   L   G   M   F   L   Y   E   Y   A   R   R   H   P   D   340

1021 TAC TCT GTC GTG CTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080
 341 Y   S   V   V   L   L   L   R   L   A   K   T   Y   E   T   T   L   E   K   C   360

1081 TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140
 361 C   A   A   A   D   P   H   E   C   Y   A   K   V   F   D   E   F   K   P   L   380

1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200
 381 V   E   E   P   Q   N   L   I   K   Q   N   C   E   L   F   E   Q   L   G   E   400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260
 401 Y   K   F   Q   N   A   L   L   V   R   Y   T   K   K   V   P   Q   V   S   T   420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320
 421 P   T   L   V   E   V   S   R   N   L   G   K   V   G   S   K   C   C   K   H   440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380
 441 P   E   A   K   R   M   P   C   A   E   D   Y   L   S   V   V   L   N   Q   L   460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440
 461 C   V   L   H   E   K   T   P   V   S   D   R   V   T   K   C   C   T   E   S   480
```

Figure 5C

```
1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
 481 L   V   N   R   R   P   C   F   S   A   L   E   V   D   E   T   Y   V   P   K   500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
 501 E   F   N   A   E   T   F   T   F   H   A   D   I   C   T   L   S   E   K   E   520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
 521 R   Q   I   K   K   Q   T   A   L   V   E   L   V   K   H   K   P   K   A   T   540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
 541 K   E   Q   L   K   A   V   M   D   D   F   A   A   F   V   E   K   C   C   K   560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
 561 A   D   D   K   E   T   C   F   A   E   E   G   K   K   L   V   A   A   S   Q   580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
 581 A   A   L   G   L   *                                   585
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Figure 5D

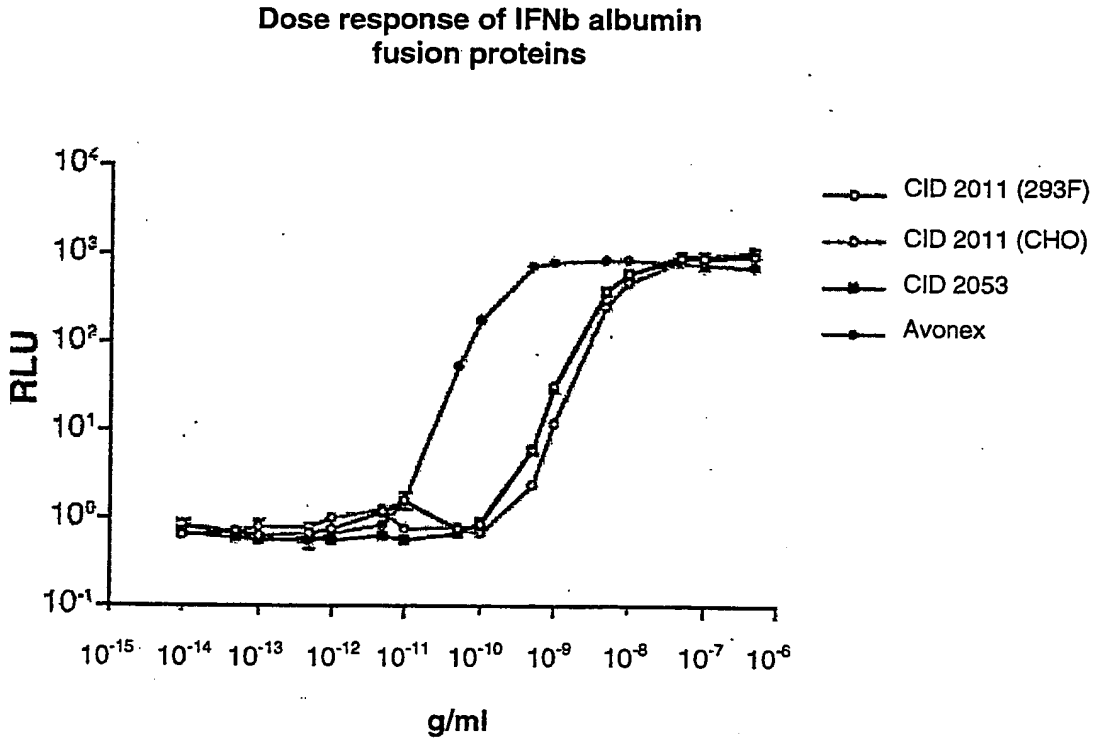

Dose response of IFNb albumin fusion proteins
RLU
10^4
10^3
10^2
10^1
10^0
10^{-1}
10^{-15} 10^{-14} 10^{-13} 10^{-12} 10^{-11} 10^{-10} 10^{-9} 10^{-8} 10^{-7} 10^{-6}
g/ml
CID 2011 (293F)
CID 2011 (CHO)
CID 2053
Avonex

Figure 6

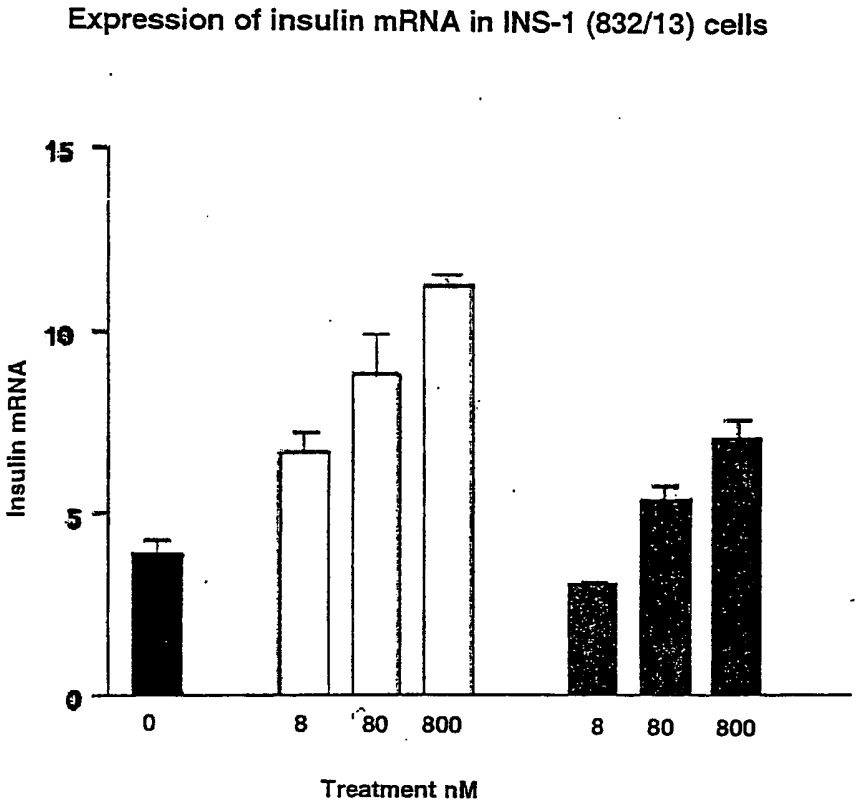
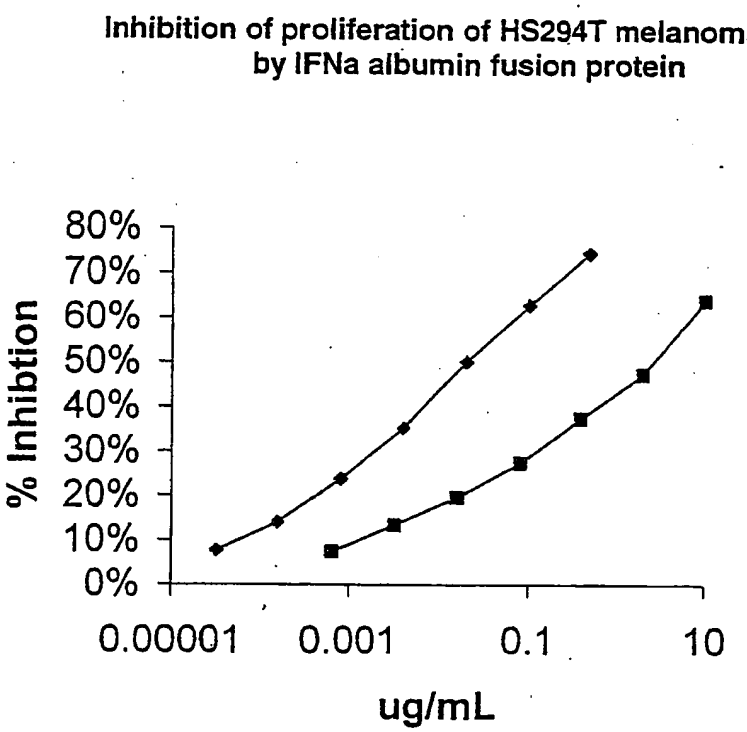

Expression of insulin mRNA in INS-1 (832/13) cells
15
10
5
0
Insulin mRNA
0
8
80
800
8
80
800
Treatment nM

Figure 7


Inhibition of proliferation of HS294T melanoma cells
by IFNa albumin fusion protein
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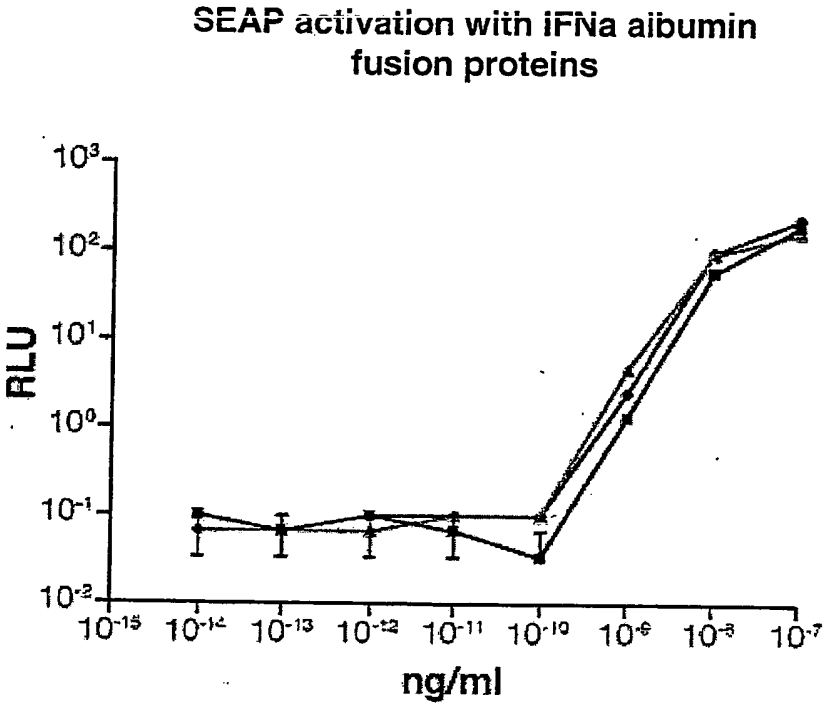
80%
70%
60%
50%
40%
30%
20%
10%
0%
0.00001
0.001
0.1
10
ug/mL

Figure 8


SEAP activation with iFNa albumin fusion proteins
RLU
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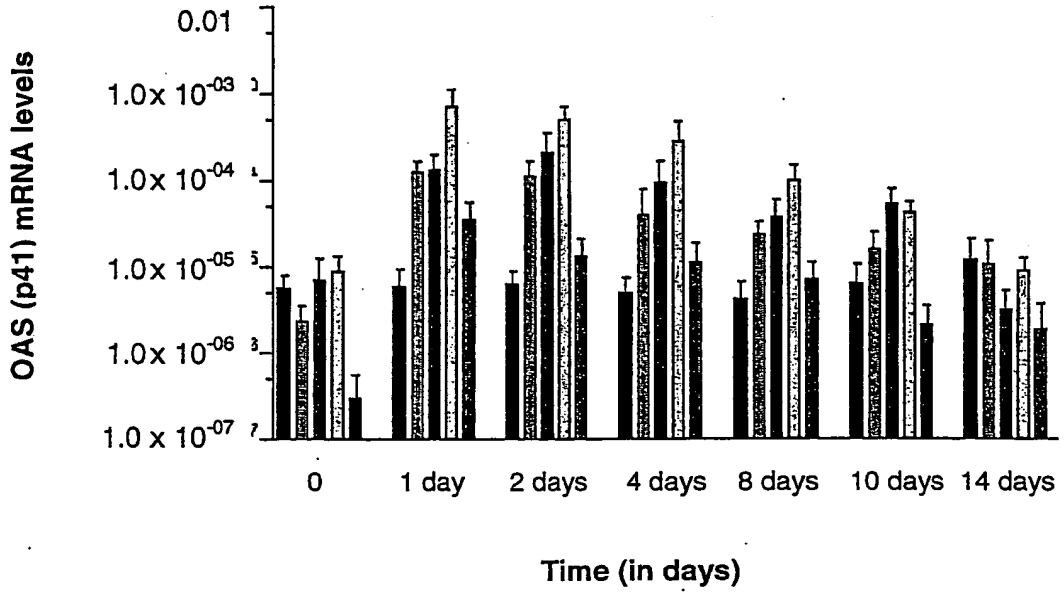
10^{2}
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-15} 10^{-14} 10^{-13} 10^{-12} 10^{-11} 10^{-10} 10^{-9} 10^{-8} 10^{-7}
ng/ml

Figure 9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1.0x 10-03
1.0x 10-04
1.0x 10-05
1.0x 10-06
1.0 x 10-07
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1 day
2 days
4 days
8 days
10 days
14 days
Time (in days)

Figure 10

<110> Human Genome Sciences, Inc.

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gcttcttgtc cacctggtgc tggtgttatt gctcctggta ctccttctca aaacactcaa 360
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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<400> 11
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
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<210> 16
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<210> 17
<211> 1386
<212> DNA
<213> Homo sapiens

<400> 17

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<211> 900
<212> DNA
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<212> DNA
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<210> 23
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<212> DNA
<213> Homo sapiens

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<211> 78
<212> DNA
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<210> 25
<211> 78
<212> DNA
<213> Homo sapiens

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<210> 26
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<212> DNA
<213> Homo sapiens

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<210> 27
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<213> Homo sapiens

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<210> 28
<211> 561
<212> DNA
<213> Homo sapiens

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<210> 29
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<212> DNA

<213> Homo sapiens

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<210> 30
<211> 501
<212> DNA
<213> Homo sapiens

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<210> 31
<211> 504
<212> DNA
<213> Homo sapiens

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<210> 32
<211> 504
<212> DNA
<213> Homo sapiens

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<210> 33
<211> 504
<212> DNA
<213> Homo sapiens

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<210> 34
<211> 498
<212> DNA
<213> Homo sapiens

<400> 34
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<210> 35
<211> 192
<212> DNA
<213> Homo sapiens

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tactgtaact aa 192

<210> 36
<211> 192
<212> DNA
<213> Homo sapiens

<400> 36
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<210> 37
<211> 177
<212> DNA
<213> Homo sapiens

<400> 37
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<210> 38
<211> 177
<212> DNA
<213> Homo sapiens

<400> 38
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<210> 39
<211> 324
<212> DNA
<213> Homo sapiens

<400> 39
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<210> 40
<211> 330
<212> DNA
<213> Homo sapiens

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<210> 41
<211> 330
<212> DNA
<213> Homo sapiens

<400> 41
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<210> 42
<211> 324
<212> DNA
<213> Homo sapiens

<400> 42
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<210> 43
<211> 324
<212> DNA
<213> Homo sapiens

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<210> 44
<211> 1290
<212> DNA
<213> Homo sapiens

<400> 44
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<210> 45
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<212> DNA
<213> Homo sapiens

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<212> DNA
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<212> DNA
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<211> 495
<212> DNA
<213> Homo sapiens

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<212> DNA
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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tgctacaacg ccagcgatca tgtctacaag ggctgcttcg acggcaacgt caccttgacg 540
gcagctaatg tgactgtgtc cttgcctgtc cggggctgtg tccaggatga attctgcact 600
cgggatggag taacaggccc agggttcacg ctcagtggct cctgttgcca ggggtcccgc 660
tgtaactctg acctccgcaa caagacctac ttctcccctc gaatcccacc ccttgtccgg 720
ctgccccctc cagagcccac gactgtggcc tcaaccacat ctgtcaccac ttctacctcg 780
gccccagtga gacccacatc caccaccaaa cccatgccag cgccaaccag tcagactccg 840
agacagggag tagaacacga ggcctcccgg gatgaggagc ccaggttgac tggaggcgcc 900
gctggccacc aggaccgcag caattcaggg cagtatcctg caaaaggggg gccccagcag 960
ccccataata aaggctgtgt ggctcccaca gctggattgg cagcccttct gttggccgtg 1020
gctgctggtg tcctactgtg a 1041

<210> 59
<211> 495
<212> DNA
<213> Homo sapiens

<400> 59
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atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 60
<211> 543
<212> DNA
<213> Homo sapiens

<400> 60
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cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 61
<211> 543
<212> DNA
<213> Homo sapiens

<400> 61
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cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 62
<211> 543
<212> DNA
<213> Homo sapiens

<400> 62
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cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 63
<211> 543
<212> DNA
<213> Homo sapiens

<400> 63
atgaaaagca tttactttgt ggctgggtta tttgtaatgc tggtacaagg cagctggcaa 60
cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 64
<211> 264
<212> DNA
<213> Homo sapiens

<400> 64
atgaaaatca tcctgtggct gtgtgttttt gggctgttcc ttgcaacttt attccctatc 60
agctggcaaa tgcctgttga atctgggttg tcttctgagg attctgcaag ctcagaaagc 120
tttgcttcga agattaagcg acatggtgaa ggaacattta ccagtgactt gtcaaaacag 180
atggaagagg aggcagtgcg gttatttatt gagtggctta agaacggagg accaagtagc 240
ggggcacctc cgccatcggg ttaa 264

<210> 65
<211> 264
<212> DNA
<213> Homo sapiens

<400> 65
atgaaaatca tcctgtggct gtgtgttttt gggctgttcc ttgcaacttt attccctatc 60
agctggcaaa tgcctgttga atctgggttg tcttctgagg attctgcaag ctcagaaagc 120
tttgcttcga agattaagcg acatggtgaa ggaacattta ccagtgactt gtcaaaacag 180
atggaagagg aggcagtgcg gttatttatt gagtggctta agaacggagg accaagtagc 240
ggggcacctc cgccatcggg ttaa 264

<210> 66
<211> 330
<212> DNA
<213> Homo sapiens

<400> 66
agcgccgggg ctggcagcca ctgtcaaaag acctccctgc gggtaaactt cgaggacatc 60
ggctgggaca gctggatcat tgcacccaag gagtatgaag cctacgagtg taagggcggc 120
tgcttcttcc ccttggctga cgatgtgacg ccgacgaaac acgctatcgt gcagaccctg 180
gtgcatctca agttccccac aaaggtgggc aaggcctgct gtgtgcccac caaactgagc 240
cccatctccg tcctctacaa ggatgacatg ggggtgccca ccctcaagta ccattacgag 300
ggcatgagcg tggcagagtg tgggtgcagg 330

<210> 67
<211> 411
<212> DNA
<213> Homo sapiens

<400> 67
atgaggacgc ctgggcctct gcccgtgctg ctgctgctcc tggcgggagc ccccgccgcg 60
cggcccactc ccccgacctg ctactcccgc atgcgggccc tgagccagga gatcacccgc 120
gacttcaacc tcctgcaggt ctcggagccc tcggagccat gtgtgagata cctgcccagg 180
ctgtacctgg acatacacaa ttactgtgtg ctggacaagc tgcgggactt tgtggcctcg 240
cccccgtgtt ggaaagtggc ccaggtagat tccttgaagg acaaagcacg gaagctgtac 300
accatcatga actcgttctg caggagagat ttggtattcc tgttggatga ctgcaatgcc 360
ttggaatacc caatcccagt gactacggtc ctgccagatc gtcagcgcta a 411

<210> 68
<211> 411
<212> DNA
<213> Homo sapiens

<400> 68
atgaggacgc ctgggcctct gcccgtgctg ctgctgctcc tggcgggagc ccccgccgcg 60
cggcccactc ccccgacctg ctactcccgc atgcgggccc tgagccagga gatcacccgc 120
gacttcaacc tcctgcaggt ctcggagccc tcggagccat gtgtgagata cctgcccagg 180
ctgtacctgg acatacacaa ttactgtgtg ctggacaagc tgcgggactt tgtggcctcg 240
cccccgtgtt ggaaagtggc ccaggtagat tccttgaagg acaaagcacg gaagctgtac 300
accatcatga actcgttctg caggagagat ttggtattcc tgttggatga ctgcaatgcc 360
ttggaatacc caatcccagt gactacggtc ctgccagatc gtcagcgcta a 411

<210> 69
<211> 561
<212> DNA
<213> Homo sapiens

<400> 69

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atgaccaaca agtgtctcct ccaaattgct ctcctgttgt gcttctccac tacagctctt     60
tccatgagct acaacttgct tggattccta caaagaagca gcaattttca gtgtcagaag    120
ctcctgtggc aattgaatgg gaggcttgaa tattgcctca aggacaggat gaactttgac    180
atccctgagg agattaagca gctgcagcag ttccagaagg aggacgccgc attgaccatc    240
tatgagatgc tccagaacat ctttgctatt ttcagacaag attcatctag cactggctgg    300
aatgagacta ttgttgagaa cctcctggct aatgtctatc atcagataaa ccatctgaag    360
acagtcctgg aagaaaaact ggagaaagaa gatttcacca ggggaaaact catgagcagt    420
ctgcacctga aaagatatta tgggaggatt ctgcattacc tgaaggccaa ggagtacagt    480
cactgtgcct ggaccatagt cagagtggaa atcctaagga acttttactt cattaacaga    540
cttacaggtt acctccgaaa c                                              561
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<210> 70
<211> 880
<212> PRT
<213> Homo sapiens

<400> 70

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Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270
```

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Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
    610                 615                 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
```

625 630 635 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
645 650 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
660 665 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
675 680 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
690 695 700

Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705 710 715 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
725 730 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
740 745 750

Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
755 760 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
770 775 780

Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785 790 795 800

Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
805 810 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
820 825 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
835 840 845

Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
850 855 860

Met Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
865 870 875 880

<210> 71
<211> 874
<212> PRT
<213> Homo sapiens

<400> 71
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

```
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                  85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
             100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
         115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
     130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
             180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
         195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
     210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
             260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
         275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
     290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
             340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
         355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
     370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
             420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
```

435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
610 615 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
625 630 635 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
645 650 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
660 665 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
675 680 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
690 695 700

Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705 710 715 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
725 730 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
740 745 750

Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
755 760 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
770 775 780

Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785 790 795 800

```
Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
                805                 810                 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
            820                 825                 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
        835                 840                 845

Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
    850                 855                 860

Met Pro Gly Leu Glu Arg Ser Val Arg Glu
865                 870
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<210> 72
<211> 868
<212> PRT
<213> Homo sapiens

<400> 72

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Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
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245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
610 615 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
625 630 635 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
645 650 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
660 665 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
675 680 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
690 695 700

Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705 710 715 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
725 730 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
740 745 750

Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
755 760 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
770 775 780

Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785 790 795 800

Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
805 810 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
820 825 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
835 840 845

Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
850 855 860

Met Pro Gly Leu
865

<210> 73
<211> 864
<212> PRT
<213> Homo sapiens

<400> 73
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val

```
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415
```

```
Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
    610                 615                 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
625                 630                 635                 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
                645                 650                 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
            660                 665                 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
        675                 680                 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
    690                 695                 700

Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705                 710                 715                 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
                725                 730                 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
            740                 745                 750

Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
        755                 760                 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
    770                 775                 780
```

```
Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785                 790                 795                 800

Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
                805                 810                 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
            820                 825                 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
        835                 840                 845

Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
    850                 855                 860
```

<210> 74
<211> 880
<212> PRT
<213> Homo sapiens

<400> 74

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240
```

```
Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605
```

```
Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
    610                 615                 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
625                 630                 635                 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
                645                 650                 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
            660                 665                 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
        675                 680                 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
    690                 695                 700

Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705                 710                 715                 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
                725                 730                 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
            740                 745                 750

Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
        755                 760                 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
    770                 775                 780

Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785                 790                 795                 800

Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
                805                 810                 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
            820                 825                 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
        835                 840                 845

Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
    850                 855                 860

Met Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
865                 870                 875                 880
```

<210> 75
<211> 880
<212> PRT
<213> Homo sapiens

<400> 75

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Val Ala Glu Thr Pro Thr Tyr Pro
            20                  25                  30

Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val Cys Ala Gln Cys Pro
        35                  40                  45
```

```
Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg Asp Ser Pro Thr Thr
     50                  55                  60

Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln Phe Trp Asn Tyr Leu
 65                  70                  75                  80

Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly Glu Arg Glu Glu Glu
                 85                  90                  95

Ala Arg Ala Cys His Ala Thr His Asn Arg Ala Cys Arg Cys Arg Thr
            100                 105                 110

Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu His Ala Ser Cys Pro
        115                 120                 125

Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro Ser Gln Asn Thr Gln
    130                 135                 140

Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala Ser Ser Ser Ser Ser
145                 150                 155                 160

Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala Leu Gly Leu Ala Leu
                165                 170                 175

Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu Cys Thr Ser Cys Thr
            180                 185                 190

Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala Glu Glu Cys Glu Arg
        195                 200                 205

Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile Ser Ile Lys Arg Leu
    210                 215                 220

Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu Gly Trp Gly Pro Thr
225                 230                 235                 240

Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys Leu Arg Arg Arg Leu
                245                 250                 255

Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu Leu Val Arg Leu Leu
            260                 265                 270

Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu Glu Arg Ser Val Arg
        275                 280                 285

Glu Arg Phe Leu Pro Val His Asp Ala His Lys Ser Glu Val Ala His
    290                 295                 300

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
305                 310                 315                 320

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
                325                 330                 335

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
            340                 345                 350

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
        355                 360                 365

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
    370                 375                 380

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
385                 390                 395                 400

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
                405                 410                 415
```

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
420 425 430

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
435 440 445

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
450 455 460

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
465 470 475 480

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
485 490 495

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
500 505 510

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
515 520 525

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
530 535 540

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
545 550 555 560

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
565 570 575

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
580 585 590

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
595 600 605

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
610 615 620

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
625 630 635 640

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
645 650 655

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
660 665 670

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
675 680 685

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
690 695 700

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
705 710 715 720

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
725 730 735

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
740 745 750

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
755 760 765

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser

```
    770                 775                 780

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
785                 790                 795                 800

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
                805                 810                 815

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
            820                 825                 830

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
        835                 840                 845

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
    850                 855                 860

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
865                 870                 875                 880
```

<210> 76
<211> 887
<212> PRT
<213> Homo sapiens

<400> 76

```
Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
  1               5                  10                  15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
            20                  25                  30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
        35                  40                  45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
    50                  55                  60

Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
65                  70                  75                  80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
                85                  90                  95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
            100                 105                 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
        115                 120                 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
    130                 135                 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145                 150                 155                 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
                165                 170                 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
            180                 185                 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
        195                 200                 205
```

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
210 215 220

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225 230 235 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
245 250 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
260 265 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
275 280 285

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His Thr Ser Asp Ala
290 295 300

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
305 310 315 320

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
325 330 335

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
340 345 350

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
355 360 365

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
370 375 380

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
385 390 395 400

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
405 410 415

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
420 425 430

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
435 440 445

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
450 455 460

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
465 470 475 480

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
485 490 495

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
500 505 510

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
515 520 525

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
530 535 540

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
545 550 555 560

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
565 570 575

```
Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
            580                 585                 590

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
        595                 600                 605

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
    610                 615                 620

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
625                 630                 635                 640

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
                645                 650                 655

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
            660                 665                 670

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
        675                 680                 685

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
    690                 695                 700

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
705                 710                 715                 720

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
                725                 730                 735

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
            740                 745                 750

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
        755                 760                 765

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
    770                 775                 780

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
785                 790                 795                 800

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
                805                 810                 815

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
            820                 825                 830

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
        835                 840                 845

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
    850                 855                 860

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
865                 870                 875                 880

Ser Gln Ala Ala Leu Gly Leu
                885
```

<210> 77
<211> 879
<212> PRT
<213> Homo sapiens

<400> 77

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
 1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
```

```
Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
    610                 615                 620

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
625                 630                 635                 640

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
                645                 650                 655

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
            660                 665                 670

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
        675                 680                 685

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
    690                 695                 700

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
705                 710                 715                 720

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
```

725 730 735

Phe Ser Ala Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
740 745 750

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
755 760 765

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
770 775 780

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
785 790 795 800

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
805 810 815

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
820 825 830

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
835 840 845

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
850 855 860

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
865 870 875

<210> 78
<211> 880
<212> PRT
<213> Homo sapiens

<400> 78
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Val Ala Glu Thr Pro Thr Tyr Pro
20 25 30

Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val Cys Ala Gln Cys Pro
35 40 45

Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg Asp Ser Pro Thr Thr
50 55 60

Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln Phe Trp Asn Tyr Leu
65 70 75 80

Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly Glu Arg Glu Glu Glu
85 90 95

Ala Arg Ala Cys His Ala Thr His Asn Arg Ala Cys Arg Cys Arg Thr
100 105 110

Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu His Ala Ser Cys Pro
115 120 125

Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro Ser Gln Asn Thr Gln
130 135 140

Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala Ser Ser Ser Ser Ser
145 150 155 160

Glu Gln Cys Gln Pro His Arg Gln Cys Thr Ala Leu Gly Leu Ala Leu
165 170 175

```
Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu Cys Thr Ser Cys Thr
            180                 185                 190

Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala Glu Glu Cys Glu Arg
        195                 200                 205

Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile Ser Ile Lys Arg Leu
    210                 215                 220

Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu Gly Trp Gly Pro Thr
225                 230                 235                 240

Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys Leu Arg Arg Arg Leu
                245                 250                 255

Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu Leu Val Arg Leu Leu
            260                 265                 270

Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu Glu Arg Ser Val Arg
        275                 280                 285

Glu Arg Phe Leu Pro Val His Asp Ala His Lys Ser Glu Val Ala His
    290                 295                 300

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
305                 310                 315                 320

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
                325                 330                 335

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
            340                 345                 350

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
        355                 360                 365

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
    370                 375                 380

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
385                 390                 395                 400

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
                405                 410                 415

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
            420                 425                 430

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
        435                 440                 445

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
    450                 455                 460

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
465                 470                 475                 480

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
                485                 490                 495

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
            500                 505                 510

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
        515                 520                 525

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
```

```
    530                 535                 540

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
545                 550                 555                 560

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
                565                 570                 575

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
            580                 585                 590

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
        595                 600                 605

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
    610                 615                 620

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
625                 630                 635                 640

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
                645                 650                 655

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
            660                 665                 670

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
        675                 680                 685

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
    690                 695                 700

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
705                 710                 715                 720

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
                725                 730                 735

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
            740                 745                 750

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
        755                 760                 765

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
    770                 775                 780

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
785                 790                 795                 800

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
                805                 810                 815

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
            820                 825                 830

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
        835                 840                 845

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
    850                 855                 860

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
865                 870                 875                 880
```

<210> 79
<211> 880

<212> PRT
<213> Homo sapiens

<400> 79
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly

```
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
    610                 615                 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
625                 630                 635                 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
                645                 650                 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
            660                 665                 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
        675                 680                 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
    690                 695                 700
```

```
Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705                 710                 715                 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
                725                 730                 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
            740                 745                 750

Gln Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
        755                 760                 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
    770                 775                 780

Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785                 790                 795                 800

Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
                805                 810                 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
            820                 825                 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
        835                 840                 845

Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
    850                 855                 860

Met Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
865                 870                 875                 880
```

<210> 80
<211> 874
<212> PRT
<213> Homo sapiens

<400> 80

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140
```

```
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510
```

```
Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Leu Glu Asp Asp Asp Lys Val Ala Glu Thr Pro Thr Tyr Pro Trp
    610                 615                 620

Arg Asp Ala Glu Thr Gly Glu Arg Leu Val Cys Ala Gln Cys Pro Pro
625                 630                 635                 640

Gly Thr Phe Val Gln Arg Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys
                645                 650                 655

Gly Pro Cys Pro Pro Arg His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu
            660                 665                 670

Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly Glu Arg Glu Glu Glu Ala
        675                 680                 685

Arg Ala Cys His Ala Thr His Asn Arg Ala Cys Arg Cys Arg Thr Gly
    690                 695                 700

Phe Phe Ala His Ala Gly Phe Cys Leu Glu His Ala Ser Cys Pro Pro
705                 710                 715                 720

Gly Ala Gly Val Ile Ala Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys
                725                 730                 735

Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu
            740                 745                 750

Gln Cys Gln Pro His Arg Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn
        755                 760                 765

Val Pro Gly Ser Ser Ser His Asp Thr Leu Cys Thr Ser Cys Thr Gly
    770                 775                 780

Phe Pro Leu Ser Thr Arg Val Pro Gly Ala Glu Glu Cys Glu Arg Ala
785                 790                 795                 800

Val Ile Asp Phe Val Ala Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln
                805                 810                 815

Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro
            820                 825                 830

Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr
        835                 840                 845

Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu Leu Val Arg Leu Leu Gln
    850                 855                 860

Ala Leu Arg Val Ala Arg Met Pro Gly Leu
```

865 870

<210> 81
<211> 870
<212> PRT
<213> Homo sapiens

<400> 81
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp

```
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Leu Glu Asp Asp Asp Lys Val Ala Glu Thr Pro Thr Tyr Pro Trp
    610                 615                 620

Arg Asp Ala Glu Thr Gly Glu Arg Leu Val Cys Ala Gln Cys Pro Pro
625                 630                 635                 640

Gly Thr Phe Val Gln Arg Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys
                645                 650                 655

Gly Pro Cys Pro Pro Arg His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu
            660                 665                 670
```

Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly Glu Arg Glu Glu Glu Ala
675 680 685

Arg Ala Cys His Ala Thr His Asn Arg Ala Cys Arg Cys Arg Thr Gly
690 695 700

Phe Phe Ala His Ala Gly Phe Cys Leu Glu His Ala Ser Cys Pro Pro
705 710 715 720

Gly Ala Gly Val Ile Ala Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys
725 730 735

Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu
740 745 750

Gln Cys Gln Pro His Arg Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn
755 760 765

Val Pro Gly Ser Ser Ser His Asp Thr Leu Cys Thr Ser Cys Thr Gly
770 775 780

Phe Pro Leu Ser Thr Arg Val Pro Gly Ala Glu Glu Cys Glu Arg Ala
785 790 795 800

Val Ile Asp Phe Val Ala Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln
805 810 815

Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro
820 825 830

Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr
835 840 845

Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu Leu Val Arg Leu Leu Gln
850 855 860

Ala Leu Arg Val Ala Arg
865 870

<210> 82
<211> 876
<212> PRT
<213> Homo sapiens

<400> 82
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

```
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480
```

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Leu Glu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu
610 615 620

Thr Gly Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val
625 630 635 640

Gln Arg Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro
645 650 655

Pro Arg His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr
660 665 670

Cys Asn Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His
675 680 685

Ala Thr His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His
690 695 700

Ala Gly Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val
705 710 715 720

Ile Ala Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro
725 730 735

Pro Gly Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro
740 745 750

His Arg Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser
755 760 765

Ser Ser His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser
770 775 780

Thr Arg Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe
785 790 795 800

Val Ala Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln
805 810 815

Ala Leu Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg
820 825 830

Ala Ala Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly

835 840 845

Ala Gln Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val
850 855 860

Ala Arg Met Pro Gly Leu Glu Arg Ser Val Arg Glu
865 870 875

<210> 83
<211> 844
<212> PRT
<213> Homo sapiens

<400> 83
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Leu Pro Ala Gln Val Ala Phe Thr
20 25 30

Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr
35 40 45

Asp Gln Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His
50 55 60

Ala Lys Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys
65 70 75 80

Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu
85 90 95

Ser Cys Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys
100 105 110

Thr Arg Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys
115 120 125

Ala Leu Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys
130 135 140

Cys Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp
145 150 155 160

Val Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser
165 170 175

Ser Thr Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile
180 185 190

Pro Gly Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr
195 200 205

Arg Ser Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr
210 215 220

Arg Ser Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser
225 230 235 240

Thr Ser Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser
245 250 255

Thr Gly Asp Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
260 265 270

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln

```
        275                 280                 285

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
    290                 295                 300

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
305                 310                 315                 320

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
                325                 330                 335

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
            340                 345                 350

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
        355                 360                 365

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
    370                 375                 380

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
385                 390                 395                 400

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
                405                 410                 415

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
            420                 425                 430

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
        435                 440                 445

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
    450                 455                 460

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
465                 470                 475                 480

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
                485                 490                 495

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
            500                 505                 510

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
        515                 520                 525

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
    530                 535                 540

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
545                 550                 555                 560

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
                565                 570                 575

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
            580                 585                 590

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
        595                 600                 605

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
    610                 615                 620

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
625                 630                 635                 640
```

```
Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
                645                 650                 655

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
            660                 665                 670

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
        675                 680                 685

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
    690                 695                 700

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
705                 710                 715                 720

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
                725                 730                 735

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
            740                 745                 750

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
        755                 760                 765

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
    770                 775                 780

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
785                 790                 795                 800

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
                805                 810                 815

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
            820                 825                 830

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
        835                 840
```

<210> 84
<211> 775
<212> PRT
<213> Homo sapiens

<400> 84

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Met Ser Tyr Asn Leu Leu Gly Phe
             20                  25                  30

Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu
         35                  40                  45

Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile
     50                  55                  60

Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala
 65                  70                  75                  80

Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln
                 85                  90                  95

Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu
            100                 105                 110
```

```
Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu
        115                 120                 125

Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu
    130                 135                 140

His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys
145                 150                 155                 160

Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg
                165                 170                 175

Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala
            180                 185                 190

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
        195                 200                 205

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
    210                 215                 220

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
225                 230                 235                 240

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
                245                 250                 255

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
            260                 265                 270

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
        275                 280                 285

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
    290                 295                 300

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
305                 310                 315                 320

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
                325                 330                 335

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
            340                 345                 350

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
        355                 360                 365

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
    370                 375                 380

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
385                 390                 395                 400

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
                405                 410                 415

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
            420                 425                 430

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
        435                 440                 445

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
    450                 455                 460

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
465                 470                 475                 480
```

```
Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
                485                 490                 495

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
            500                 505                 510

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
        515                 520                 525

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
    530                 535                 540

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
545                 550                 555                 560

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
                565                 570                 575

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
            580                 585                 590

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
        595                 600                 605

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
    610                 615                 620

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
625                 630                 635                 640

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
                645                 650                 655

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
            660                 665                 670

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
        675                 680                 685

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
    690                 695                 700

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
705                 710                 715                 720

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
                725                 730                 735

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
            740                 745                 750

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
        755                 760                 765

Ser Gln Ala Ala Leu Gly Leu
    770                 775
```

<210> 85
<211> 775
<212> PRT
<213> Homo sapiens

<400> 85

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15
```

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys

370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe
610 615 620

Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys
625 630 635 640

Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu
645 650 655

Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu
660 665 670

Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp
675 680 685

Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile
690 695 700

Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe
705 710 715 720

Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly
725 730 735

```
Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp
            740                 745                 750

Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg
        755                 760                 765

Leu Thr Gly Tyr Leu Arg Asn
    770                 775
```

<210> 86
<211> 844
<212> PRT
<213> Homo sapiens

<400> 86

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
```

```
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly
    610                 615                 620

Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys
625                 630                 635                 640
```

Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys
645 650 655

Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln
660 665 670

Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser
675 680 685

Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile
690 695 700

Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly
705 710 715 720

Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val
725 730 735

Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala
740 745 750

Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro
755 760 765

His Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Met Asp
770 775 780

Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala
785 790 795 800

Val His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro
805 810 815

Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met
820 825 830

Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp
835 840

<210> 87
<211> 880
<212> PRT
<213> Homo sapiens

<400> 87
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln

```
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480
```

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
610 615 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
625 630 635 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
645 650 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
660 665 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
675 680 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
690 695 700

Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705 710 715 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
725 730 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
740 745 750

Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
755 760 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
770 775 780

Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785 790 795 800

Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
805 810 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
820 825 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
835 840 845

```
Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
    850                 855                 860

Met Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
865                 870                 875                 880
```

<210> 88
<211> 885
<212> PRT
<213> Homo sapiens

<400> 88

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Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
  1               5                  10                  15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
            20                  25                  30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
        35                  40                  45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
    50                  55                  60

Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
65                  70                  75                  80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
                85                  90                  95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
            100                 105                 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
        115                 120                 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
    130                 135                 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145                 150                 155                 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
                165                 170                 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
            180                 185                 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
        195                 200                 205

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
    210                 215                 220

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225                 230                 235                 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
                245                 250                 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
            260                 265                 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
        275                 280                 285
```

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His Asp Ala His Lys
290 295 300

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
305 310 315 320

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
325 330 335

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
340 345 350

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
355 360 365

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
370 375 380

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
385 390 395 400

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
405 410 415

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
420 425 430

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
435 440 445

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
450 455 460

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
465 470 475 480

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
485 490 495

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
500 505 510

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
515 520 525

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
530 535 540

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
545 550 555 560

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
565 570 575

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
580 585 590

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
595 600 605

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
610 615 620

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
625 630 635 640

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr

645 650 655

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
660 665 670

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
675 680 685

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
690 695 700

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
705 710 715 720

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
725 730 735

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
740 745 750

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
755 760 765

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
770 775 780

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
785 790 795 800

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
805 810 815

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
820 825 830

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
835 840 845

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
850 855 860

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
865 870 875 880

Ala Ala Leu Gly Leu
885

<210> 89
<211> 885
<212> PRT
<213> Homo sapiens

<400> 89
Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
1 5 10 15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
20 25 30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
35 40 45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
50 55 60

Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
65 70 75 80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
85 90 95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
100 105 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
115 120 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
130 135 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145 150 155 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
165 170 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
180 185 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
195 200 205

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
210 215 220

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225 230 235 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
245 250 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
260 265 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
275 280 285

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His Asp Ala His Lys
290 295 300

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
305 310 315 320

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
325 330 335

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
340 345 350

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
355 360 365

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
370 375 380

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
385 390 395 400

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
405 410 415

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
420 425 430

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr

435 440 445

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
450 455 460

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
465 470 475 480

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
485 490 495

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
500 505 510

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
515 520 525

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
530 535 540

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
545 550 555 560

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
565 570 575

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
580 585 590

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
595 600 605

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
610 615 620

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
625 630 635 640

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
645 650 655

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
660 665 670

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
675 680 685

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
690 695 700

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
705 710 715 720

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
725 730 735

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
740 745 750

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
755 760 765

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
770 775 780

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
785 790 795 800

```
Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
                805                 810                 815

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
            820                 825                 830

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
        835                 840                 845

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
    850                 855                 860

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
865                 870                 875                 880

Ala Ala Leu Gly Leu
                885
```

<210> 90
<211> 880
<212> PRT
<213> Homo sapiens

<400> 90

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220
```

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly
610 615 620

Glu Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg
625 630 635 640

Pro Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg
645 650 655

His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn
660 665 670

Val Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr
675 680 685

His Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly
690 695 700

Phe Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala
705 710 715 720

Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly
725 730 735

Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg
740 745 750

Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser
755 760 765

His Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg
770 775 780

Val Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala
785 790 795 800

Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu
805 810 815

Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala
820 825 830

Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln
835 840 845

Asp Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg
850 855 860

Met Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
865 870 875 880

<210> 91
<211> 635
<212> PRT
<213> Homo sapiens

<400> 91
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Asp Arg Leu His Cys Lys Pro
20 25 30

```
Gln Arg Gln Ser Pro Trp Met Lys Cys Gln His Leu Asp Pro Glu Gly
        35                  40                  45

Gly Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
    50                  55                  60

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
65                  70                  75                  80

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
                85                  90                  95

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
            100                 105                 110

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
        115                 120                 125

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
    130                 135                 140

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
145                 150                 155                 160

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
                165                 170                 175

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
            180                 185                 190

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
        195                 200                 205

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
    210                 215                 220

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
225                 230                 235                 240

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
                245                 250                 255

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
            260                 265                 270

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
        275                 280                 285

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
    290                 295                 300

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
305                 310                 315                 320

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
                325                 330                 335

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
            340                 345                 350

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
        355                 360                 365

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
    370                 375                 380

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
385                 390                 395                 400
```

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
405 410 415

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
420 425 430

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
435 440 445

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
450 455 460

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
465 470 475 480

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
485 490 495

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
500 505 510

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
515 520 525

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
530 535 540

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
545 550 555 560

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
565 570 575

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
580 585 590

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
595 600 605

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
610 615 620

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 92
<211> 635
<212> PRT
<213> Homo sapiens

<400> 92
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

```
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
```

```
Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Gly Asp Arg Leu His Cys Lys Pro Gln Arg Gln Ser Pro Trp Met
    610                 615                 620

Lys Cys Gln His Leu Asp Pro Glu Gly Gly Gly
625                 630                 635
```

<210> 93
<211> 635
<212> PRT
<213> Homo sapiens

<400> 93

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Asp Asp Asp Asp Cys Gly Trp
            20                  25                  30

Ile Gly Phe Ala Asn Phe His Leu Cys Leu His Gly Asp Pro Glu Gly
        35                  40                  45

Gly Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
    50                  55                  60

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
65                  70                  75                  80

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
                85                  90                  95

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
            100                 105                 110

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
        115                 120                 125
```

```
Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
    130                 135                 140

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
145                 150                 155                 160

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
                165                 170                 175

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
            180                 185                 190

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
        195                 200                 205

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
    210                 215                 220

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
225                 230                 235                 240

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
                245                 250                 255

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
            260                 265                 270

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
        275                 280                 285

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
    290                 295                 300

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
305                 310                 315                 320

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
                325                 330                 335

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
            340                 345                 350

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
        355                 360                 365

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
    370                 375                 380

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
385                 390                 395                 400

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
                405                 410                 415

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
            420                 425                 430

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
        435                 440                 445

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
    450                 455                 460

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
465                 470                 475                 480

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
```

485 490 495

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
500 505 510

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
515 520 525

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
530 535 540

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
545 550 555 560

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
565 570 575

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
580 585 590

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
595 600 605

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
610 615 620

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 94
<211> 635
<212> PRT
<213> Homo sapiens

<400> 94
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro

```
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525
```

```
Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Gly Asp Asp Asp Asp Cys Gly Trp Ile Gly Phe Ala Asn Phe His
    610                 615                 620

Leu Cys Leu His Gly Asp Pro Glu Gly Gly Gly
625                 630                 635
```

<210> 95
<211> 772
<212> PRT
<213> Homo sapiens

<400> 95

```
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
  1               5                  10                  15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
            20                  25                  30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
        35                  40                  45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
    50                  55                  60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65                  70                  75                  80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
                85                  90                  95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
            100                 105                 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
        115                 120                 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
    130                 135                 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145                 150                 155                 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
                165                 170                 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser
            180                 185                 190

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
        195                 200                 205
```

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
210 215 220

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys
225 230 235 240

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
245 250 255

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly
260 265 270

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
275 280 285

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
290 295 300

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
305 310 315 320

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
325 330 335

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
340 345 350

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
355 360 365

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
370 375 380

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
385 390 395 400

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
405 410 415

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
420 425 430

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
435 440 445

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
450 455 460

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
465 470 475 480

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
485 490 495

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
500 505 510

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
515 520 525

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
530 535 540

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
545 550 555 560

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
565 570 575

```
Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
            580                 585                 590

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
        595                 600                 605

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
    610                 615                 620

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
625                 630                 635                 640

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
                645                 650                 655

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
            660                 665                 670

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
        675                 680                 685

Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
    690                 695                 700

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
705                 710                 715                 720

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
                725                 730                 735

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
            740                 745                 750

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
        755                 760                 765

Ala Leu Gly Leu
    770
```

<210> 96
<211> 775
<212> PRT
<213> Homo sapiens

<400> 96

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110
```

```
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
```

```
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe
    610                 615                 620

Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys
625                 630                 635                 640

Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu
                645                 650                 655

Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu
            660                 665                 670

Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp
        675                 680                 685

Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile
    690                 695                 700

Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe
705                 710                 715                 720

Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly
                725                 730                 735

Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp
            740                 745                 750

Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg
        755                 760                 765

Leu Thr Gly Tyr Leu Arg Asn
    770                 775
```

<210> 97
<211> 772
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (240)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (270)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 97

```
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
  1               5                  10                  15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
            20                  25                  30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
        35                  40                  45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
    50                  55                  60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65                  70                  75                  80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
                85                  90                  95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
            100                 105                 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
        115                 120                 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
    130                 135                 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145                 150                 155                 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
                165                 170                 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser
            180                 185                 190

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
        195                 200                 205

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
    210                 215                 220

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Xaa
225                 230                 235                 240

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
                245                 250                 255

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Xaa Tyr Gly
            260                 265                 270

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
        275                 280                 285

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
    290                 295                 300

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
305                 310                 315                 320
```

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
325 330 335

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
340 345 350

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
355 360 365

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
370 375 380

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
385 390 395 400

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
405 410 415

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
420 425 430

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
435 440 445

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
450 455 460

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
465 470 475 480

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
485 490 495

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
500 505 510

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
515 520 525

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
530 535 540

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
545 550 555 560

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
565 570 575

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
580 585 590

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
595 600 605

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
610 615 620

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
625 630 635 640

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
645 650 655

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
660 665 670

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
675 680 685

```
Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
    690                 695                 700

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
705                 710                 715                 720

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
                725                 730                 735

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
            740                 745                 750

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
        755                 760                 765

Ala Leu Gly Leu
    770
```

<210> 98
<211> 775
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (487)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 98

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190
```

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Xaa His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

```
Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe
    610                 615                 620

Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys
625                 630                 635                 640

Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu
                645                 650                 655

Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu
            660                 665                 670

Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp
        675                 680                 685

Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile
    690                 695                 700

Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe
705                 710                 715                 720

Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly
                725                 730                 735

Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp
            740                 745                 750

Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg
        755                 760                 765

Leu Thr Gly Tyr Leu Arg Asn
    770                 775


<210> 99
<211> 752
<212> PRT
<213> Homo sapiens

<400> 99
Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu
  1               5                  10                  15

Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys
             20                  25                  30

Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
         35                  40                  45

Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
     50                  55                  60

Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
 65                  70                  75                  80

Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
                 85                  90                  95
```

Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
100 105 110

Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
115 120 125

Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
130 135 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
145 150 155 160

Leu Asp Leu Ser Pro Gly Cys Asp Ala His Lys Ser Glu Val Ala His
165 170 175

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
180 185 190

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
195 200 205

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
210 215 220

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
225 230 235 240

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
245 250 255

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
260 265 270

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
275 280 285

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
290 295 300

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
305 310 315 320

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
325 330 335

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
340 345 350

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
355 360 365

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
370 375 380

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
385 390 395 400

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
405 410 415

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
420 425 430

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
435 440 445

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
450 455 460

```
Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
465                 470                 475                 480

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
                485                 490                 495

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
            500                 505                 510

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
        515                 520                 525

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
    530                 535                 540

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
545                 550                 555                 560

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
                565                 570                 575

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
            580                 585                 590

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
        595                 600                 605

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
    610                 615                 620

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
625                 630                 635                 640

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
                645                 650                 655

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
            660                 665                 670

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
        675                 680                 685

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
    690                 695                 700

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
705                 710                 715                 720

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
                725                 730                 735

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            740                 745                 750
```

<210> 100
<211> 755
<212> PRT
<213> Homo sapiens

```
<400> 100
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30
```

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu

385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys Thr Leu Ile Lys
610 615 620

Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr Gln Ser Val Ser
625 630 635 640

Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro Gly Leu His Pro
645 650 655

Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala Val Tyr Gln Gln
660 665 670

Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln Ile Ser Asn Asp
675 680 685

Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala Phe Ser Lys Ser
690 695 700

Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu Asp Ser Leu Gly
705 710 715 720

Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val Val Ala Leu Ser
725 730 735

Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln Leu Asp Leu Ser
740 745 750

Pro Gly Cys
755

<210> 101
<211> 755
<212> PRT
<213> Homo sapiens

<400> 101
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Val Pro Ile Gln Lys Val Gln Asp
20 25 30

Asp Thr Lys Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile
35 40 45

Ser His Thr Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp
50 55 60

Phe Ile Pro Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln
65 70 75 80

Thr Leu Ala Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn
85 90 95

Val Ile Gln Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His
100 105 110

Val Leu Ala Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu
115 120 125

Glu Thr Leu Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser
130 135 140

Thr Glu Val Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met
145 150 155 160

Leu Trp Gln Leu Asp Leu Ser Pro Gly Cys Asp Ala His Lys Ser Glu
165 170 175

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
180 185 190

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
195 200 205

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
210 215 220

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
225 230 235 240

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
245 250 255

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
260 265 270

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
275 280 285

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
290 295 300

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr

305 310 315 320

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
325 330 335

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
340 345 350

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
355 360 365

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
370 375 380

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
385 390 395 400

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
405 410 415

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
420 425 430

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
435 440 445

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
450 455 460

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
465 470 475 480

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
485 490 495

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
500 505 510

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
515 520 525

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
530 535 540

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
545 550 555 560

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
565 570 575

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
580 585 590

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
595 600 605

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
610 615 620

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
625 630 635 640

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
645 650 655

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
660 665 670

```
Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
        675                 680                 685

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
    690                 695                 700

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
705                 710                 715                 720

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
                725                 730                 735

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
            740                 745                 750

Leu Gly Leu
        755
```

<210> 102
<211> 755
<212> PRT
<213> Homo sapiens

<400> 102

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220
```

```
Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590
```

```
Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys Thr Leu Ile Lys
    610                 615                 620

Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr Gln Ser Val Ser
625                 630                 635                 640

Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro Gly Leu His Pro
                645                 650                 655

Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala Val Tyr Gln Gln
            660                 665                 670

Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln Ile Ser Asn Asp
        675                 680                 685

Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala Phe Ser Lys Ser
    690                 695                 700

Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu Asp Ser Leu Gly
705                 710                 715                 720

Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val Val Ala Leu Ser
                725                 730                 735

Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln Leu Asp Leu Ser
            740                 745                 750

Pro Gly Cys
        755
```

<210> 103
<211> 774
<212> PRT
<213> Homo sapiens

<400> 103

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Cys Asp Leu Pro Gln Thr His Ser
             20                  25                  30

Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile
         35                  40                  45

Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln
     50                  55                  60

Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu
 65                  70                  75                  80

His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser
                 85                  90                  95

Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu
            100                 105                 110

Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly
        115                 120                 125

Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg
    130                 135                 140
```

```
Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser
145                 150                 155                 160

Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser
                165                 170                 175

Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His
            180                 185                 190

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
        195                 200                 205

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
    210                 215                 220

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
225                 230                 235                 240

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
                245                 250                 255

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
            260                 265                 270

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
        275                 280                 285

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
    290                 295                 300

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
305                 310                 315                 320

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
                325                 330                 335

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
            340                 345                 350

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
        355                 360                 365

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
    370                 375                 380

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
385                 390                 395                 400

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
                405                 410                 415

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
            420                 425                 430

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
        435                 440                 445

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
    450                 455                 460

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
465                 470                 475                 480

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
                485                 490                 495

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
            500                 505                 510
```

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
515 520 525

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
530 535 540

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
545 550 555 560

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
565 570 575

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
580 585 590

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
595 600 605

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
610 615 620

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
625 630 635 640

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
645 650 655

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
660 665 670

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
675 680 685

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
690 695 700

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
705 710 715 720

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
725 730 735

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
740 745 750

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
755 760 765

Gln Ala Ala Leu Gly Leu
770

<210> 104
<211> 672
<212> PRT
<213> Homo sapiens

<400> 104
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

```
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
 50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
```

405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu
610 615 620

Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly
625 630 635 640

Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln
645 650 655

Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
660 665 670

<210> 105
<211> 672
<212> PRT
<213> Homo sapiens

<400> 105
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Val Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly
20 25 30

Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe
35 40 45

Phe Tyr Thr Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro
50 55 60

Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr
65 70 75 80

Gln Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His
85 90 95

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
100 105 110

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
115 120 125

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
130 135 140

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
145 150 155 160

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
165 170 175

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
180 185 190

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
195 200 205

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
210 215 220

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
225 230 235 240

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
245 250 255

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
260 265 270

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
275 280 285

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
290 295 300

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
305 310 315 320

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
325 330 335

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
340 345 350

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
355 360 365

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
370 375 380

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
385 390 395 400

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
405 410 415

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu

420 425 430

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
435 440 445

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
450 455 460

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
465 470 475 480

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
485 490 495

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
500 505 510

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
515 520 525

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
530 535 540

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
545 550 555 560

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
565 570 575

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
580 585 590

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
595 600 605

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
610 615 620

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
625 630 635 640

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
645 650 655

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 106
<211> 667
<212> PRT
<213> Homo sapiens

<400> 106
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

```
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
```

435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu
610 615 620

Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly
625 630 635 640

Gly Gly Pro Gly Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile
645 650 655

Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
660 665

<210> 107
<211> 667
<212> PRT
<213> Homo sapiens

<400> 107
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly
20 25 30

Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe
35 40 45

Phe Tyr Thr Pro Lys Thr Gly Gly Gly Pro Gly Lys Arg Gly Ile Val
50 55 60

Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr
65 70 75 80

Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu

85 90 95

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
100 105 110

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
115 120 125

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
130 135 140

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
145 150 155 160

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
165 170 175

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
180 185 190

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
195 200 205

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
210 215 220

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
225 230 235 240

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
245 250 255

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
260 265 270

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
275 280 285

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
290 295 300

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
305 310 315 320

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
325 330 335

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
340 345 350

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
355 360 365

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
370 375 380

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
385 390 395 400

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
405 410 415

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
420 425 430

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
435 440 445

```
His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
    450                 455                 460

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
465                 470                 475                 480

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
                485                 490                 495

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
            500                 505                 510

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
        515                 520                 525

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
    530                 535                 540

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
545                 550                 555                 560

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
                565                 570                 575

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
            580                 585                 590

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
        595                 600                 605

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
    610                 615                 620

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
625                 630                 635                 640

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
                645                 650                 655

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 108
<211> 699
<212> PRT
<213> Homo sapiens

<400> 108

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1                 5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Lys Thr Leu Cys Ser Met Glu Glu
            20                  25                  30

Ala Ile Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg
        35                  40                  45

Ala Ile Ser Ser Ile Gly Leu Glu Cys Gln Ser Val Thr Ser Arg Gly
    50                  55                  60

Asp Leu Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys
65                  70                  75                  80

Gly Ser Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His
                85                  90                  95

Cys Gln Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val
```

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           100                 105                 110

Gln Pro Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
        115                 120                 125

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
    130                 135                 140

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
145                 150                 155                 160

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
                165                 170                 175

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
            180                 185                 190

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
        195                 200                 205

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
    210                 215                 220

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
225                 230                 235                 240

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
                245                 250                 255

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
            260                 265                 270

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
        275                 280                 285

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
    290                 295                 300

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
305                 310                 315                 320

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
                325                 330                 335

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
            340                 345                 350

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
        355                 360                 365

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
    370                 375                 380

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
385                 390                 395                 400

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
                405                 410                 415

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
            420                 425                 430

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
        435                 440                 445

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
    450                 455                 460
```

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
465 470 475 480

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
485 490 495

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
500 505 510

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
515 520 525

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
530 535 540

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
545 550 555 560

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
565 570 575

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
580 585 590

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
595 600 605

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
610 615 620

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
625 630 635 640

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
645 650 655

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
660 665 670

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
675 680 685

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
690 695

<210> 109
<211> 699
<212> PRT
<213> Homo sapiens

<400> 109
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

```
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
```

```
Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
     450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile Gln
    610                 615                 620

Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly Leu
625                 630                 635                 640

Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro Arg
                645                 650                 655

Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser Trp
            660                 665                 670

Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met Asp
        675                 680                 685

Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
    690                 695


<210> 110
<211> 114
<212> PRT
<213> Homo sapiens

<400> 110
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Lys Thr Leu Cys Ser Met Glu Glu
            20                  25                  30

Ala Ile Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg
        35                  40                  45

Ala Ile Ser Ser Ile Gly Leu Glu Cys Gln Ser Val Thr Ser Arg Gly
    50                  55                  60
```

Asp Leu Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys
65 70 75 80

Gly Ser Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His
85 90 95

Cys Gln Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val
100 105 110

Gln Pro

<210> 111
<211> 693
<212> PRT
<213> Homo sapiens

<400> 111
Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val
1 5 10 15

Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
20 25 30

Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
35 40 45

Leu Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
50 55 60

Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
65 70 75 80

Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
85 90 95

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro Asp Ala His Lys
100 105 110

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
115 120 125

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
130 135 140

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
145 150 155 160

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
165 170 175

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
180 185 190

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
195 200 205

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
210 215 220

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
225 230 235 240

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
245 250 255

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala

260 265 270

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
275 280 285

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
290 295 300

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
305 310 315 320

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
325 330 335

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
340 345 350

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
355 360 365

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
370 375 380

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
385 390 395 400

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
405 410 415

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
420 425 430

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
435 440 445

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
450 455 460

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
465 470 475 480

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
485 490 495

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
500 505 510

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
515 520 525

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
530 535 540

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
545 550 555 560

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
565 570 575

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
580 585 590

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
595 600 605

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
610 615 620

```
Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
625                 630                 635                 640

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
                645                 650                 655

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
            660                 665                 670

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
        675                 680                 685

Ala Ala Leu Gly Leu
    690
```

<210> 112
<211> 693
<212> PRT
<213> Homo sapiens

<400> 112

```
Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val
  1               5                  10                  15

Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
             20                  25                  30

Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
         35                  40                  45

Leu Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
     50                  55                  60

Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
 65                  70                  75                  80

Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
                 85                  90                  95

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro Asp Ala His Lys
            100                 105                 110

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
        115                 120                 125

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
    130                 135                 140

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
145                 150                 155                 160

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
                165                 170                 175

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
            180                 185                 190

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
        195                 200                 205

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
    210                 215                 220

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
225                 230                 235                 240
```

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
245 250 255

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
260 265 270

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
275 280 285

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
290 295 300

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
305 310 315 320

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
325 330 335

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
340 345 350

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
355 360 365

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
370 375 380

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
385 390 395 400

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
405 410 415

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
420 425 430

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
435 440 445

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
450 455 460

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
465 470 475 480

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
485 490 495

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
500 505 510

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
515 520 525

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
530 535 540

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
545 550 555 560

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
565 570 575

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
580 585 590

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
595 600 605

```
Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
    610                 615                 620

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
625                 630                 635                 640

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
                645                 650                 655

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
            660                 665                 670

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
        675                 680                 685

Ala Ala Leu Gly Leu
    690
```

<210> 113
<211> 1016
<212> PRT
<213> Homo sapiens

<400> 113

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Lys Pro Leu Gln Ser Trp Gly Arg
            20                  25                  30

Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly
        35                  40                  45

Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val
    50                  55                  60

Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln
65                  70                  75                  80

Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn
                85                  90                  95

Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg
            100                 105                 110

Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe
        115                 120                 125

Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His
    130                 135                 140

Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn
145                 150                 155                 160

His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp
                165                 170                 175

Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr
            180                 185                 190

Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu
        195                 200                 205

Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser
    210                 215                 220
```

Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp
225 230 235 240

Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe
245 250 255

Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu
260 265 270

Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys
275 280 285

Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu
290 295 300

Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys
305 310 315 320

Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val
325 330 335

Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu
340 345 350

Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp
355 360 365

Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu
370 375 380

Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu
385 390 395 400

Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu
405 410 415

Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg Asp
420 425 430

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
435 440 445

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
450 455 460

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
465 470 475 480

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
485 490 495

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
500 505 510

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
515 520 525

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
530 535 540

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
545 550 555 560

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
565 570 575

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
580 585 590

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
595 600 605

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
610 615 620

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
625 630 635 640

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
645 650 655

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
660 665 670

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
675 680 685

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
690 695 700

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
705 710 715 720

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
725 730 735

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
740 745 750

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
755 760 765

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
770 775 780

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
785 790 795 800

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
805 810 815

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
820 825 830

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
835 840 845

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
850 855 860

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
865 870 875 880

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
885 890 895

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
900 905 910

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
915 920 925

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
930 935 940

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu

945 950 955 960

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
965 970 975

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
980 985 990

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
995 1000 1005

Ala Ser Gln Ala Ala Leu Gly Leu
1010 1015

<210> 114
<211> 1016
<212> PRT
<213> Homo sapiens

<400> 114
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser

245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala
610 615 620

His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu Pro Glu His Thr Phe
625 630 635 640

Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val Asp Phe Leu Arg Ser
645 650 655

Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys Thr Arg Val Glu Pro
660 665 670

Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser
675 680 685

Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe Ser Met Glu Asp Ala
690 695 700

Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe Gln Lys His Ile Leu
705 710 715 720

Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln Ile Thr Arg Ala Glu
725 730 735

Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val Asp Pro Ser His Asp
740 745 750

Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala
755 760 765

Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu Val Ser Gln Asp Ile
770 775 780

Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser Ser Ala Val Lys Arg
785 790 795 800

Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn Lys Leu Glu Val Thr
805 810 815

Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu Asp Ile Ser Val Pro
820 825 830

Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val Phe Ser Asn Asp His
835 840 845

Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu Arg Glu Met Ile Ser
850 855 860

His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr
865 870 875 880

Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr Asp Gly His Val Ala
885 890 895

Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser
900 905 910

His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe Glu Asp Ile Gly Trp
915 920 925

Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys
930 935 940

Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val Thr Pro Thr Lys His
945 950 955 960

Ala Ile Val Gln Thr Leu Val His Leu Lys Phe Pro Thr Lys Val Gly
965 970 975

Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr
980 985 990

Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr His Tyr Glu Gly Met
995 1000 1005

Ser Val Ala Glu Cys Gly Cys Arg
1010 1015

<210> 115
<211> 769
<212> PRT
<213> Homo sapiens

<400> 115
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
20 25 30

Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys
35 40 45

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
50 55 60

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
65 70 75 80

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
85 90 95

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
100 105 110

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
115 120 125

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
130 135 140

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
145 150 155 160

Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu
165 170 175

Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu Val Ala
180 185 190

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
195 200 205

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
210 215 220

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
225 230 235 240

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
245 250 255

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
260 265 270

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
275 280 285

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
290 295 300

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
305 310 315 320

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
325 330 335

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
340 345 350

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
355 360 365

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
370 375 380

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
385 390 395 400

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
405 410 415

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
420 425 430

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
435 440 445

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
450 455 460

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
465 470 475 480

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
485 490 495

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
500 505 510

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
515 520 525

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
530 535 540

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
545 550 555 560

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
565 570 575

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
580 585 590

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
595 600 605

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
610 615 620

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val

625 630 635 640

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
645 650 655

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
660 665 670

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
675 680 685

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
690 695 700

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
705 710 715 720

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
725 730 735

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
740 745 750

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
755 760 765

Leu

<210> 116
<211> 716
<212> PRT
<213> Homo sapiens

<400> 116
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr
20 25 30

Ser Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile
35 40 45

Ala Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe
50 55 60

Pro Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr
65 70 75 80

Leu Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val
85 90 95

Pro Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly
100 105 110

Val Pro Thr Leu Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys
115 120 125

Gly Cys Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
130 135 140

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
145 150 155 160

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
165 170 175

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
180 185 190

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
195 200 205

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
210 215 220

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
225 230 235 240

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
245 250 255

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
260 265 270

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
275 280 285

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
290 295 300

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
305 310 315 320

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
325 330 335

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
340 345 350

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
355 360 365

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
370 375 380

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
385 390 395 400

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
405 410 415

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
420 425 430

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
435 440 445

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
450 455 460

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
465 470 475 480

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
485 490 495

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
500 505 510

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
515 520 525

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
530 535 540

```
Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
545                 550                 555                 560

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
                565                 570                 575

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
            580                 585                 590

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
        595                 600                 605

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
    610                 615                 620

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
625                 630                 635                 640

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
                645                 650                 655

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
            660                 665                 670

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
        675                 680                 685

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
    690                 695                 700

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
705                 710                 715
```

<210> 117
<211> 719
<212> PRT
<213> Homo sapiens

```
<400> 117
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140
```

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe

```
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val
    610                 615                 620

Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu
625                 630                 635                 640

Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp
                645                 650                 655

Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu
            660                 665                 670

Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu
        675                 680                 685

Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu
    690                 695                 700

Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
705                 710                 715


<210> 118
<211> 1016
<212> PRT
<213> Homo sapiens

<400> 118
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Lys Pro Leu Gln Ser Trp Gly Arg
             20                  25                  30

Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly
         35                  40                  45

Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val
     50                  55                  60

Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln
 65                  70                  75                  80

Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn
                 85                  90                  95

Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg
            100                 105                 110
```

Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe
115 120 125

Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His
130 135 140

Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn
145 150 155 160

His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp
165 170 175

Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr
180 185 190

Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu
195 200 205

Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser
210 215 220

Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp
225 230 235 240

Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe
245 250 255

Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu
260 265 270

Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys
275 280 285

Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu
290 295 300

Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys
305 310 315 320

Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val
325 330 335

Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu
340 345 350

Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp
355 360 365

Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu
370 375 380

Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu
385 390 395 400

Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu
405 410 415

Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg Asp
420 425 430

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
435 440 445

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
450 455 460

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe

```
465                 470                 475                 480

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
                485                 490                 495

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
            500                 505                 510

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
        515                 520                 525

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
    530                 535                 540

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
545                 550                 555                 560

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
                565                 570                 575

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
            580                 585                 590

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
        595                 600                 605

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
    610                 615                 620

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
625                 630                 635                 640

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
                645                 650                 655

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
            660                 665                 670

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
        675                 680                 685

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
    690                 695                 700

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
705                 710                 715                 720

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
                725                 730                 735

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
            740                 745                 750

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
        755                 760                 765

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
    770                 775                 780

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
785                 790                 795                 800

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
                805                 810                 815

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
            820                 825                 830
```

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
835 840 845

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
850 855 860

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
865 870 875 880

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
885 890 895

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
900 905 910

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
915 920 925

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
930 935 940

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
945 950 955 960

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
965 970 975

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
980 985 990

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
995 1000 1005

Ala Ser Gln Ala Ala Leu Gly Leu
1010 1015

<210> 119
<211> 1016
<212> PRT
<213> Homo sapiens

<400> 119
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

```
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495
```

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala
610 615 620

His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu Pro Glu His Thr Phe
625 630 635 640

Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val Asp Phe Leu Arg Ser
645 650 655

Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys Thr Arg Val Glu Pro
660 665 670

Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser
675 680 685

Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe Ser Met Glu Asp Ala
690 695 700

Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe Gln Lys His Ile Leu
705 710 715 720

Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln Ile Thr Arg Ala Glu
725 730 735

Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val Asp Pro Ser His Asp
740 745 750

Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala
755 760 765

Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu Val Ser Gln Asp Ile
770 775 780

Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser Ser Ala Val Lys Arg
785 790 795 800

Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn Lys Leu Glu Val Thr
805 810 815

Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu Asp Ile Ser Val Pro
820 825 830

Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val Phe Ser Asn Asp His
835 840 845

Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu Arg Glu Met Ile Ser

```
    850                 855                 860

His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr
865                 870                 875                 880

Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr Asp Gly His Val Ala
                885                 890                 895

Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser
            900                 905                 910

His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe Glu Asp Ile Gly Trp
        915                 920                 925

Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys
    930                 935                 940

Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val Thr Pro Thr Lys His
945                 950                 955                 960

Ala Ile Val Gln Thr Leu Val His Leu Lys Phe Pro Thr Lys Val Gly
                965                 970                 975

Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr
            980                 985                 990

Lys Asp Asp Met Gly Val Pro Thr  Leu Lys Tyr His Tyr  Glu Gly Met
        995                 1000                1005

Ser Val  Ala Glu Cys Gly Cys  Arg
    1010                1015
```

<210> 120
<211> 835
<212> PRT
<213> Homo sapiens

<400> 120

```
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
  1               5                  10                  15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
             20                  25                  30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
         35                  40                  45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
     50                  55                  60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
 65                  70                  75                  80

Ser Leu Asp Lys Arg Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser
                 85                  90                  95

Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe
            100                 105                 110

Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe
        115                 120                 125

Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met
    130                 135                 140

Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala
```

```
145                 150                 155                 160

Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln
                165                 170                 175

Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu
            180                 185                 190

Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe
        195                 200                 205

Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala
    210                 215                 220

Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr
225                 230                 235                 240

Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu
                245                 250                 255

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
            260                 265                 270

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
        275                 280                 285

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
    290                 295                 300

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
305                 310                 315                 320

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
                325                 330                 335

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
            340                 345                 350

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
        355                 360                 365

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
    370                 375                 380

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
385                 390                 395                 400

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
                405                 410                 415

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
            420                 425                 430

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
        435                 440                 445

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
    450                 455                 460

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
465                 470                 475                 480

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
                485                 490                 495

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
            500                 505                 510
```

```
Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
        515                 520                 525

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
    530                 535                 540

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
545                 550                 555                 560

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
                565                 570                 575

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
            580                 585                 590

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
        595                 600                 605

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
    610                 615                 620

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
625                 630                 635                 640

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
                645                 650                 655

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
            660                 665                 670

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
        675                 680                 685

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
    690                 695                 700

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
705                 710                 715                 720

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
                725                 730                 735

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
            740                 745                 750

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
        755                 760                 765

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
    770                 775                 780

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
785                 790                 795                 800

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
                805                 810                 815

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
            820                 825                 830

Leu Gly Leu
        835
```

<210> 121
<211> 716
<212> PRT

<213> Homo sapiens

<400> 121

```
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
 1               5                  10                  15

Leu Gly Ser Gln Ala Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr
            20                  25                  30

Ser Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile
        35                  40                  45

Ala Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe
    50                  55                  60

Pro Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr
65                  70                  75                  80

Leu Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val
                85                  90                  95

Pro Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly
            100                 105                 110

Val Pro Thr Leu Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys
        115                 120                 125

Gly Cys Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
    130                 135                 140

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
145                 150                 155                 160

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
                165                 170                 175

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
            180                 185                 190

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
        195                 200                 205

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
    210                 215                 220

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
225                 230                 235                 240

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
                245                 250                 255

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
            260                 265                 270

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
        275                 280                 285

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
    290                 295                 300

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
305                 310                 315                 320

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
                325                 330                 335

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
            340                 345                 350
```

```
Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
        355                 360                 365

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
    370                 375                 380

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
385                 390                 395                 400

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
                405                 410                 415

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
            420                 425                 430

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
        435                 440                 445

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
    450                 455                 460

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
465                 470                 475                 480

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
                485                 490                 495

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
            500                 505                 510

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
        515                 520                 525

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
    530                 535                 540

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
545                 550                 555                 560

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
                565                 570                 575

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
            580                 585                 590

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
        595                 600                 605

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
    610                 615                 620

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
625                 630                 635                 640

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
                645                 650                 655

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
            660                 665                 670

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
        675                 680                 685

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
    690                 695                 700

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
```

705 710 715

<210> 122
<211> 1014
<212> PRT
<213> Homo sapiens

<400> 122
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
1 5 10 15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
20 25 30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
35 40 45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
50 55 60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65 70 75 80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
85 90 95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
100 105 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
115 120 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
130 135 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145 150 155 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
165 170 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
180 185 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
195 200 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
210 215 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225 230 235 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
245 250 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
260 265 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
275 280 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
290 295 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser

305 310 315 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
325 330 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
340 345 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
355 360 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
370 375 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385 390 395 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg Asp Ala His
420 425 430

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
435 440 445

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
450 455 460

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
465 470 475 480

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
485 490 495

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
500 505 510

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
515 520 525

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
530 535 540

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
545 550 555 560

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
565 570 575

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
580 585 590

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
595 600 605

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
610 615 620

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
625 630 635 640

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
645 650 655

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
660 665 670

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
675 680 685

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
690 695 700

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
705 710 715 720

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
725 730 735

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
740 745 750

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
755 760 765

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
770 775 780

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
785 790 795 800

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
805 810 815

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
820 825 830

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
835 840 845

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
850 855 860

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
865 870 875 880

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
885 890 895

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
900 905 910

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
915 920 925

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
930 935 940

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
945 950 955 960

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
965 970 975

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
980 985 990

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
995 1000 1005

Gln Ala Ala Leu Gly Leu
1010

<210> 123
<211> 1014
<212> PRT
<213> Homo sapiens

<400> 123

```
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
            20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
    50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335
```

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
340 345 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
355 360 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
370 375 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385 390 395 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg Asp Ala His
420 425 430

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
435 440 445

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
450 455 460

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
465 470 475 480

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
485 490 495

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
500 505 510

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
515 520 525

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
530 535 540

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
545 550 555 560

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
565 570 575

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
580 585 590

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
595 600 605

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
610 615 620

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
625 630 635 640

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
645 650 655

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
660 665 670

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
675 680 685

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu

690 695 700

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
705 710 715 720

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
725 730 735

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
740 745 750

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
755 760 765

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
770 775 780

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
785 790 795 800

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
805 810 815

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
820 825 830

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
835 840 845

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
850 855 860

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
865 870 875 880

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
885 890 895

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
900 905 910

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
915 920 925

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
930 935 940

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
945 950 955 960

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
965 970 975

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
980 985 990

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
995 1000 1005

Gln Ala Ala Leu Gly Leu
1010

<210> 124
<211> 774
<212> PRT
<213> Homo sapiens

<400> 124
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val

355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705 710 715 720

```
Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
        755                 760                 765

Ser Leu Arg Ser Lys Glu
    770
```

<210> 125
<211> 773
<212> PRT
<213> Homo sapiens

<400> 125

```
Met Ala Leu Thr Phe Ala Leu Leu Val Ala Leu Leu Val Leu Ser Cys
  1               5                  10                  15

Lys Ser Ser Cys Ser Val Gly Cys Asp Leu Pro Gln Thr His Ser Leu
            20                  25                  30

Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser
        35                  40                  45

Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu
    50                  55                  60

Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His
65                  70                  75                  80

Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser
                85                  90                  95

Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr
            100                 105                 110

Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val
        115                 120                 125

Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys
    130                 135                 140

Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro
145                 150                 155                 160

Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu
                165                 170                 175

Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys
            180                 185                 190

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
        195                 200                 205

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
    210                 215                 220

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
225                 230                 235                 240

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
                245                 250                 255
```

```
Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
            260                 265                 270

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
        275                 280                 285

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
    290                 295                 300

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
305                 310                 315                 320

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
                325                 330                 335

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
            340                 345                 350

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
        355                 360                 365

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
    370                 375                 380

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
385                 390                 395                 400

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
                405                 410                 415

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
            420                 425                 430

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
        435                 440                 445

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
    450                 455                 460

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
465                 470                 475                 480

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
                485                 490                 495

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
            500                 505                 510

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
        515                 520                 525

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
    530                 535                 540

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
545                 550                 555                 560

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
                565                 570                 575

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
            580                 585                 590

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
        595                 600                 605

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
    610                 615                 620
```

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
625 630 635 640

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
645 650 655

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
660 665 670

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
675 680 685

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
690 695 700

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
705 710 715 720

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
725 730 735

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
740 745 750

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
755 760 765

Ala Ala Leu Gly Leu
770

<210> 126
<211> 908
<212> PRT
<213> Homo sapiens

<400> 126
Met Asp Pro Ala Arg Lys Ala Gly Ala Gln Ala Met Ile Trp Thr Ala
1 5 10 15

Gly Trp Leu Leu Leu Leu Leu Leu Arg Gly Gly Ala Gln Ala Leu Glu
20 25 30

Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro Asn Lys
35 40 45

Met Lys Thr Val Lys Cys Ala Pro Gly Val Asp Val Cys Thr Glu Ala
50 55 60

Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Leu Ala Val Arg
65 70 75 80

Gly Cys Gly Ser Gly Leu Pro Gly Lys Asn Asp Arg Gly Leu Asp Leu
85 90 95

His Gly Leu Leu Ala Phe Ile Gln Leu Gln Gln Cys Ala Gln Asp Arg
100 105 110

Cys Asn Ala Lys Leu Asn Leu Thr Ser Arg Ala Leu Asp Pro Ala Gly
115 120 125

Asn Glu Ser Ala Tyr Pro Pro Asn Gly Val Glu Cys Tyr Ser Cys Val
130 135 140

Gly Leu Ser Arg Glu Ala Cys Gln Gly Thr Ser Pro Pro Val Val Ser
145 150 155 160

```
Cys Tyr Asn Ala Ser Asp His Val Tyr Lys Gly Cys Phe Asp Gly Asn
                165                 170                 175

Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val Arg Gly
            180                 185                 190

Cys Val Gln Asp Glu Phe Cys Thr Arg Asp Gly Val Thr Gly Pro Gly
        195                 200                 205

Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Ser Arg Cys Asn Ser Asp
    210                 215                 220

Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu Val Arg
225                 230                 235                 240

Leu Pro Pro Pro Glu Pro Thr Thr Val Ala Ser Thr Thr Ser Val Thr
                245                 250                 255

Thr Ser Thr Ser Ala Pro Val Arg Pro Thr Ser Thr Thr Lys Pro Met
            260                 265                 270

Pro Ala Pro Thr Ser Gln Thr Pro Arg Gln Gly Val Glu His Glu Ala
        275                 280                 285

Ser Arg Asp Glu Glu Pro Arg Leu Thr Gly Gly Ala Ala Gly His Gln
    290                 295                 300

Asp Arg Ser Asn Ser Gly Gln Tyr Pro Ala Lys Gly Gly Pro Gln Gln
305                 310                 315                 320

Pro His Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
                325                 330                 335

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
            340                 345                 350

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
        355                 360                 365

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
    370                 375                 380

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
385                 390                 395                 400

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
                405                 410                 415

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
            420                 425                 430

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
        435                 440                 445

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
    450                 455                 460

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
465                 470                 475                 480

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
                485                 490                 495

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
            500                 505                 510

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
        515                 520                 525
```

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
530 535 540

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
545 550 555 560

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
565 570 575

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
580 585 590

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
595 600 605

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
610 615 620

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
625 630 635 640

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
645 650 655

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
660 665 670

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
675 680 685

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
690 695 700

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
705 710 715 720

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
725 730 735

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
740 745 750

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
755 760 765

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
770 775 780

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
785 790 795 800

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
805 810 815

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
820 825 830

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
835 840 845

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
850 855 860

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
865 870 875 880

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys

```
                885                 890                 895

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            900                 905
```

<210> 127
<211> 908
<212> PRT
<213> Homo sapiens

<400> 127

```
Met Asp Pro Ala Arg Lys Ala Gly Ala Gln Ala Met Ile Trp Thr Ala
  1               5                  10                  15

Gly Trp Leu Leu Leu Leu Leu Leu Arg Gly Gly Ala Gln Ala Leu Glu
             20                  25                  30

Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro Asn Lys
         35                  40                  45

Met Lys Thr Val Lys Cys Ala Pro Gly Val Asp Val Cys Thr Glu Ala
     50                  55                  60

Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Leu Ala Val Arg
 65                  70                  75                  80

Gly Cys Gly Ser Gly Leu Pro Gly Lys Asn Asp Arg Gly Leu Asp Leu
                 85                  90                  95

His Gly Leu Leu Ala Phe Ile Gln Leu Gln Gln Cys Ala Gln Asp Arg
            100                 105                 110

Cys Asn Ala Lys Leu Asn Leu Thr Ser Arg Ala Leu Asp Pro Ala Gly
        115                 120                 125

Asn Glu Ser Ala Tyr Pro Pro Asn Gly Val Glu Cys Tyr Ser Cys Val
    130                 135                 140

Gly Leu Ser Arg Glu Ala Cys Gln Gly Thr Ser Pro Pro Val Val Ser
145                 150                 155                 160

Cys Tyr Asn Ala Ser Asp His Val Tyr Lys Gly Cys Phe Asp Gly Asn
                165                 170                 175

Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val Arg Gly
            180                 185                 190

Cys Val Gln Asp Glu Phe Cys Thr Arg Asp Gly Val Thr Gly Pro Gly
        195                 200                 205

Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Ser Arg Cys Asn Ser Asp
    210                 215                 220

Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu Val Arg
225                 230                 235                 240

Leu Pro Pro Pro Glu Pro Thr Thr Val Ala Ser Thr Thr Ser Val Thr
                245                 250                 255

Thr Ser Thr Ser Ala Pro Val Arg Pro Thr Ser Thr Thr Lys Pro Met
            260                 265                 270

Pro Ala Pro Thr Ser Gln Thr Pro Arg Gln Gly Val Glu His Glu Ala
        275                 280                 285

Ser Arg Asp Glu Glu Pro Arg Leu Thr Gly Gly Ala Ala Gly His Gln
```

290 295 300

Asp Arg Ser Asn Ser Gly Gln Tyr Pro Ala Lys Gly Gly Pro Gln Gln
305 310 315 320

Pro His Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
325 330 335

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
340 345 350

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
355 360 365

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
370 375 380

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
385 390 395 400

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
405 410 415

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
420 425 430

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
435 440 445

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
450 455 460

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
465 470 475 480

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
485 490 495

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
500 505 510

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
515 520 525

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
530 535 540

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
545 550 555 560

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
565 570 575

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
580 585 590

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
595 600 605

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
610 615 620

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
625 630 635 640

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
645 650 655

```
Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
            660                 665                 670

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
        675                 680                 685

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
    690                 695                 700

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
705                 710                 715                 720

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
                725                 730                 735

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
            740                 745                 750

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
        755                 760                 765

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
    770                 775                 780

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
785                 790                 795                 800

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
                805                 810                 815

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
            820                 825                 830

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
        835                 840                 845

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
    850                 855                 860

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
865                 870                 875                 880

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
                885                 890                 895

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            900                 905
```

<210> 128
<211> 769
<212> PRT
<213> Homo sapiens

<400> 128

```
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
  1               5                  10                  15

Ile Ser Ala Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
             20                  25                  30

Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys
         35                  40                  45

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
     50                  55                  60
```

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
65 70 75 80

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
85 90 95

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
100 105 110

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
115 120 125

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
130 135 140

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
145 150 155 160

Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu
165 170 175

Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu Val Ala
180 185 190

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
195 200 205

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
210 215 220

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
225 230 235 240

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
245 250 255

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
260 265 270

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
275 280 285

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
290 295 300

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
305 310 315 320

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
325 330 335

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
340 345 350

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
355 360 365

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
370 375 380

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
385 390 395 400

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
405 410 415

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
420 425 430

```
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        435                 440                 445

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    450                 455                 460

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
465                 470                 475                 480

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                485                 490                 495

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            500                 505                 510

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        515                 520                 525

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    530                 535                 540

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
545                 550                 555                 560

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                565                 570                 575

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            580                 585                 590

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        595                 600                 605

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    610                 615                 620

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
625                 630                 635                 640

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                645                 650                 655

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            660                 665                 670

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        675                 680                 685

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    690                 695                 700

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
705                 710                 715                 720

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                725                 730                 735

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            740                 745                 750

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        755                 760                 765

Leu
```

<210> 129

<211> 639
<212> PRT
<213> Homo sapiens

<400> 129

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg His Ala Glu Gly Thr Phe Thr Ser
            20                  25                  30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
        35                  40                  45

Trp Leu Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg
    50                  55                  60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65                  70                  75                  80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
                85                  90                  95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
            100                 105                 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
        115                 120                 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
    130                 135                 140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145                 150                 155                 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                165                 170                 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180                 185                 190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195                 200                 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210                 215                 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225                 230                 235                 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245                 250                 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260                 265                 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275                 280                 285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290                 295                 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305                 310                 315                 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                325                 330                 335
```

```
Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            340                 345                 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        355                 360                 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    370                 375                 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385                 390                 395                 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                405                 410                 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            420                 425                 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        435                 440                 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    450                 455                 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465                 470                 475                 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                485                 490                 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            500                 505                 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        515                 520                 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    530                 535                 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545                 550                 555                 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                565                 570                 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            580                 585                 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        595                 600                 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    610                 615                 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635
```

<210> 130
<211> 639
<212> PRT
<213> Homo sapiens

<400> 130

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
```

```
                20                  25                  30
His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
            35                  40                  45
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
        50                  55                  60
Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95
Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160
Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190
Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205
Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220
Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240
Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255
Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285
Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300
Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320
Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335
Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350
Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380
```

```
Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
    610                 615                 620

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
625                 630                 635


<210> 131
<211> 639
<212> PRT
<213> Homo sapiens

<400> 131
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser
             20                  25                  30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
         35                  40                  45

Trp Leu Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg
     50                  55                  60
```

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65 70 75 80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
85 90 95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
100 105 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
115 120 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
130 135 140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145 150 155 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
165 170 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
180 185 190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
195 200 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
210 215 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225 230 235 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
245 250 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
260 265 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
275 280 285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
290 295 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305 310 315 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
325 330 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
340 345 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
355 360 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
370 375 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385 390 395 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
405 410 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
420 425 430

```
Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        435                 440                 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    450                 455                 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465                 470                 475                 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                485                 490                 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            500                 505                 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        515                 520                 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    530                 535                 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545                 550                 555                 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                565                 570                 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            580                 585                 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        595                 600                 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    610                 615                 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635
```

<210> 132
<211> 639
<212> PRT
<213> Homo sapiens

<400> 132

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110
```

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val

```
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
    610                 615                 620

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
625                 630                 635


<210> 133
<211> 648
<212> PRT
<213> Homo sapiens

<400> 133
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
```

145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

```
Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu
    610                 615                 620

Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro
625                 630                 635                 640

Ser Ser Gly Ala Pro Pro Pro Ser
                645
```

<210> 134
<211> 648
<212> PRT
<213> Homo sapiens

<400> 134

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser
            20                  25                  30

Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu
        35                  40                  45

Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Asp
    50                  55                  60

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
65                  70                  75                  80

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
                85                  90                  95

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
            100                 105                 110

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
        115                 120                 125

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
    130                 135                 140

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
145                 150                 155                 160

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
                165                 170                 175
```

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
180 185 190

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
195 200 205

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
210 215 220

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
225 230 235 240

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
245 250 255

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
260 265 270

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
275 280 285

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
290 295 300

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
305 310 315 320

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
325 330 335

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
340 345 350

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
355 360 365

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
370 375 380

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
385 390 395 400

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
405 410 415

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
420 425 430

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
435 440 445

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
450 455 460

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
465 470 475 480

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
485 490 495

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
500 505 510

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
515 520 525

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
530 535 540

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
545 550 555 560

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
565 570 575

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
580 585 590

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
595 600 605

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
610 615 620

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
625 630 635 640

Ala Ser Gln Ala Ala Leu Gly Leu
645

<210> 135
<211> 1018
<212> PRT
<213> Homo sapiens

<400> 135
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
1 5 10 15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
20 25 30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
35 40 45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
50 55 60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65 70 75 80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
85 90 95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
100 105 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
115 120 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
130 135 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145 150 155 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
165 170 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
180 185 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
195 200 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
210 215 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225 230 235 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
245 250 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
260 265 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
275 280 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
290 295 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Leu
305 310 315 320

Glu Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
325 330 335

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
340 345 350

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
355 360 365

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
370 375 380

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
385 390 395 400

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
405 410 415

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
420 425 430

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
435 440 445

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
450 455 460

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
465 470 475 480

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
485 490 495

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
500 505 510

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
515 520 525

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
530 535 540

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
545 550 555 560

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp

565 570 575

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
580 585 590

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
595 600 605

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
610 615 620

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
625 630 635 640

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
645 650 655

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
660 665 670

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
675 680 685

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
690 695 700

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
705 710 715 720

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
725 730 735

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
740 745 750

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
755 760 765

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
770 775 780

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
785 790 795 800

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
805 810 815

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
820 825 830

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
835 840 845

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
850 855 860

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
865 870 875 880

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
885 890 895

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Leu Glu Ser Ala Gly Ala
900 905 910

Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe Glu Asp Ile
915 920 925

```
Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu Ala Tyr Glu
    930                 935                 940

Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val Thr Pro Thr
945                 950                 955                 960

Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe Pro Thr Lys
                965                 970                 975

Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro Ile Ser Val
            980                 985                 990

Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr His Tyr Glu
        995                 1000                1005

Gly Met Ser Val Ala Glu Cys Gly Cys Arg
    1010                1015
```

<210> 136
<211> 726
<212> PRT
<213> Homo sapiens

<400> 136

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220
```

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Arg Pro Thr Pro Pro Thr Cys Tyr Ser Arg Met Arg Ala Leu
610 615 620

Ser Gln Glu Ile Thr Arg Asp Phe Asn Leu Leu Gln Val Ser Glu Pro
625 630 635 640

Ser Glu Pro Cys Val Arg Tyr Leu Pro Arg Leu Tyr Leu Asp Ile His
645 650 655

Asn Tyr Cys Val Leu Asp Lys Leu Arg Asp Phe Val Ala Ser Pro Pro
660 665 670

Cys Trp Lys Val Ala Gln Val Asp Ser Leu Lys Asp Lys Ala Arg Lys
675 680 685

Leu Tyr Thr Ile Met Asn Ser Phe Cys Arg Arg Asp Leu Val Phe Leu
690 695 700

Leu Asp Asp Cys Asn Ala Leu Glu Tyr Pro Ile Pro Val Thr Thr Val
705 710 715 720

Leu Pro Asp Arg Gln Arg
725

<210> 137
<211> 726
<212> PRT
<213> Homo sapiens

<400> 137
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Arg Pro Thr Pro Pro Thr Cys
20 25 30

Tyr Ser Arg Met Arg Ala Leu Ser Gln Glu Ile Thr Arg Asp Phe Asn
35 40 45

Leu Leu Gln Val Ser Glu Pro Ser Glu Pro Cys Val Arg Tyr Leu Pro
50 55 60

Arg Leu Tyr Leu Asp Ile His Asn Tyr Cys Val Leu Asp Lys Leu Arg
65 70 75 80

Asp Phe Val Ala Ser Pro Pro Cys Trp Lys Val Ala Gln Val Asp Ser
85 90 95

Leu Lys Asp Lys Ala Arg Lys Leu Tyr Thr Ile Met Asn Ser Phe Cys
100 105 110

Arg Arg Asp Leu Val Phe Leu Leu Asp Asp Cys Asn Ala Leu Glu Tyr
115 120 125

Pro Ile Pro Val Thr Thr Val Leu Pro Asp Arg Gln Arg Asp Ala His
130 135 140

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
145 150 155 160

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
165 170 175

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
180 185 190

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
195 200 205

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
210 215 220

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
225 230 235 240

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
245 250 255

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
260 265 270

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
275 280 285

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
290 295 300

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
305 310 315 320

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
325 330 335

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
340 345 350

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
355 360 365

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
370 375 380

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
385 390 395 400

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
405 410 415

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
420 425 430

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
435 440 445

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
450 455 460

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
465 470 475 480

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
485 490 495

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
500 505 510

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
515 520 525

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
530 535 540

```
Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
545                 550                 555                 560

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
                565                 570                 575

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
            580                 585                 590

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
        595                 600                 605

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
    610                 615                 620

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
625                 630                 635                 640

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
                645                 650                 655

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
            660                 665                 670

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
        675                 680                 685

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
    690                 695                 700

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
705                 710                 715                 720

Gln Ala Ala Leu Gly Leu
                725
```

<210> 138
<211> 771
<212> PRT
<213> Homo sapiens

<400> 138

```
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
  1               5                  10                  15

Thr Thr Ala Leu Ser Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser
             20                  25                  30

Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu
         35                  40                  45

Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile
     50                  55                  60

Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr
 65                  70                  75                  80

Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser
                 85                  90                  95

Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr
            100                 105                 110

His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys
        115                 120                 125
```

```
Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg
    130                 135                 140

Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His
145                 150                 155                 160

Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe
                165                 170                 175

Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser Glu
            180                 185                 190

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
        195                 200                 205

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
    210                 215                 220

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
225                 230                 235                 240

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
                245                 250                 255

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
            260                 265                 270

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
        275                 280                 285

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
    290                 295                 300

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
305                 310                 315                 320

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
                325                 330                 335

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
            340                 345                 350

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
        355                 360                 365

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
    370                 375                 380

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
385                 390                 395                 400

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
                405                 410                 415

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
            420                 425                 430

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
        435                 440                 445

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
    450                 455                 460

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
465                 470                 475                 480

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
```

485 490 495

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
500 505 510

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
515 520 525

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
530 535 540

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
545 550 555 560

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
565 570 575

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
580 585 590

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
595 600 605

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
610 615 620

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
625 630 635 640

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
645 650 655

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
660 665 670

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
675 680 685

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
690 695 700

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
705 710 715 720

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
725 730 735

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
740 745 750

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
755 760 765

Leu Gly Leu
770

<210> 139
<211> 271
<212> PRT
<213> Homo sapiens

<400> 139
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
1 5 10 15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
20 25 30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
35 40 45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
50 55 60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65 70 75 80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
85 90 95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
100 105 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
115 120 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
130 135 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145 150 155 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
165 170 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
180 185 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
195 200 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
210 215 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225 230 235 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
245 250 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
260 265 270

<210> 140
<211> 271
<212> PRT
<213> Homo sapiens

<400> 140
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
1 5 10 15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
20 25 30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
35 40 45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
50 55 60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65 70 75 80

```
Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270
```

<210> 141
<211> 271
<212> PRT
<213> Homo sapiens

<400> 141

```
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
  1               5                  10                  15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
            20                  25                  30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
        35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
    50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125
```

```
Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270
```

<210> 142
<211> 271
<212> PRT
<213> Homo sapiens

<400> 142

```
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
  1               5                  10                  15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
            20                  25                  30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
        35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
    50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
```

165 170 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
180 185 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
195 200 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
210 215 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225 230 235 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
245 250 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
260 265 270

<210> 143
<211> 271
<212> PRT
<213> Homo sapiens

<400> 143
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
1 5 10 15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
20 25 30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
35 40 45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
50 55 60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65 70 75 80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
85 90 95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
100 105 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
115 120 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
130 135 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145 150 155 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
165 170 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
180 185 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
195 200 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
210 215 220

```
Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270


<210> 144
<211> 271
<212> PRT
<213> Homo sapiens

<400> 144
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
  1               5                  10                  15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
            20                  25                  30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
        35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
    50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270
```

<210> 145
<211> 300
<212> PRT
<213> Homo sapiens

<400> 145
Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
1 5 10 15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
20 25 30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
35 40 45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
50 55 60

Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
65 70 75 80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
85 90 95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
100 105 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
115 120 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
130 135 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145 150 155 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
165 170 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
180 185 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
195 200 205

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
210 215 220

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225 230 235 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
245 250 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
260 265 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
275 280 285

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
290 295 300

<210> 146
<211> 271
<212> PRT

<213> Homo sapiens

<400> 146
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
1 5 10 15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
20 25 30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
35 40 45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
50 55 60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65 70 75 80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
85 90 95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
100 105 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
115 120 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
130 135 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145 150 155 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
165 170 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
180 185 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
195 200 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
210 215 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225 230 235 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
245 250 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
260 265 270

<210> 147
<211> 271
<212> PRT
<213> Homo sapiens

<400> 147
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
1 5 10 15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
20 25 30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His

```
        35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
     50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
 65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                 85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270
```

<210> 148
<211> 271
<212> PRT
<213> Homo sapiens

<400> 148

```
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
  1               5                  10                  15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
            20                  25                  30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
        35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
     50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
 65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
```

```
                85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270
```

<210> 149
<211> 271
<212> PRT
<213> Homo sapiens

<400> 149

```
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
  1               5                  10                  15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
             20                  25                  30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
         35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
     50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
 65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                 85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140
```

```
Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270
```

<210> 150
<211> 271
<212> PRT
<213> Homo sapiens

<400> 150

```
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
  1               5                  10                  15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
            20                  25                  30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
        35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
    50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
```

```
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270
```

<210> 151
<211> 300
<212> PRT
<213> Homo sapiens

<400> 151

```
Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
  1               5                  10                  15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
             20                  25                  30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
         35                  40                  45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
     50                  55                  60

Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
 65                  70                  75                  80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
                 85                  90                  95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
            100                 105                 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
        115                 120                 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
    130                 135                 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145                 150                 155                 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
                165                 170                 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
            180                 185                 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
        195                 200                 205

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
    210                 215                 220
```

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225 230 235 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
245 250 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
260 265 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
275 280 285

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
290 295 300

<210> 152
<211> 461
<212> PRT
<213> Homo sapiens

<400> 152
Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu
1 5 10 15

Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr
20 25 30

Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln
35 40 45

Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys
50 55 60

Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp
65 70 75 80

Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys
85 90 95

Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg
100 105 110

Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu
115 120 125

Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg
130 135 140

Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val
145 150 155 160

Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr
165 170 175

Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly
180 185 190

Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser
195 200 205

Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser
210 215 220

Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser
225 230 235 240

```
Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly
                245                 250                 255

Asp Phe Ala Leu Pro Val Gly Leu Ile Val Gly Val Thr Ala Leu Gly
            260                 265                 270

Leu Leu Ile Ile Gly Val Val Asn Cys Val Ile Met Thr Gln Val Lys
        275                 280                 285

Lys Lys Pro Leu Cys Leu Gln Arg Glu Ala Lys Val Pro His Leu Pro
    290                 295                 300

Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln His Leu Leu
305                 310                 315                 320

Ile Thr Ala Pro Ser Ser Ser Ser Ser Ser Leu Glu Ser Ser Ala Ser
                325                 330                 335

Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly
            340                 345                 350

Val Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser
        355                 360                 365

Asp Ser Ser Pro Gly Gly His Gly Thr Gln Val Asn Val Thr Cys Ile
    370                 375                 380

Val Asn Val Cys Ser Ser Ser Asp His Ser Ser Gln Cys Ser Ser Gln
385                 390                 395                 400

Ala Ser Ser Thr Met Gly Asp Thr Asp Ser Ser Pro Ser Glu Ser Pro
                405                 410                 415

Lys Asp Glu Gln Val Pro Phe Ser Lys Glu Glu Cys Ala Phe Arg Ser
            420                 425                 430

Gln Leu Glu Thr Pro Glu Thr Leu Leu Gly Ser Thr Glu Glu Lys Pro
        435                 440                 445

Leu Pro Leu Gly Val Pro Asp Ala Gly Met Lys Pro Ser
    450                 455                 460
```

<210> 153
<211> 166
<212> PRT
<213> Homo sapiens

<400> 153

```
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
  1               5                  10                  15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
            20                  25                  30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
        35                  40                  45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
    50                  55                  60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65                  70                  75                  80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
                85                  90                  95
```

```
His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165
```

<210> 154
<211> 166
<212> PRT
<213> Homo sapiens

<400> 154

```
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
  1               5                  10                  15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
            20                  25                  30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
        35                  40                  45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
    50                  55                  60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65                  70                  75                  80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
                85                  90                  95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165
```

<210> 155
<211> 461
<212> PRT
<213> Homo sapiens

<400> 155

```
Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu
  1               5                  10                  15
```

```
Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr
                20                  25                  30

Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln
        35                  40                  45

Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys
    50                  55                  60

Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp
65                  70                  75                  80

Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys
                85                  90                  95

Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg
            100                 105                 110

Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu
        115                 120                 125

Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg
    130                 135                 140

Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val
145                 150                 155                 160

Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr
                165                 170                 175

Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly
            180                 185                 190

Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser
        195                 200                 205

Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser
    210                 215                 220

Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser
225                 230                 235                 240

Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly
                245                 250                 255

Asp Phe Ala Leu Pro Val Gly Leu Ile Val Gly Val Thr Ala Leu Gly
            260                 265                 270

Leu Leu Ile Ile Gly Val Val Asn Cys Val Ile Met Thr Gln Val Lys
        275                 280                 285

Lys Lys Pro Leu Cys Leu Gln Arg Glu Ala Lys Val Pro His Leu Pro
    290                 295                 300

Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln His Leu Leu
305                 310                 315                 320

Ile Thr Ala Pro Ser Ser Ser Ser Ser Ser Leu Glu Ser Ser Ala Ser
                325                 330                 335

Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly
            340                 345                 350

Val Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser
        355                 360                 365

Asp Ser Ser Pro Gly Gly His Gly Thr Gln Val Asn Val Thr Cys Ile
    370                 375                 380
```

```
Val Asn Val Cys Ser Ser Ser Asp His Ser Ser Gln Cys Ser Ser Gln
385                 390                 395                 400

Ala Ser Ser Thr Met Gly Asp Thr Asp Ser Ser Pro Ser Glu Ser Pro
                405                 410                 415

Lys Asp Glu Gln Val Pro Phe Ser Lys Glu Glu Cys Ala Phe Arg Ser
            420                 425                 430

Gln Leu Glu Thr Pro Glu Thr Leu Leu Gly Ser Thr Glu Glu Lys Pro
        435                 440                 445

Leu Pro Leu Gly Val Pro Asp Ala Gly Met Lys Pro Ser
    450                 455                 460
```

<210> 156
<211> 271
<212> PRT
<213> Homo sapiens

<400> 156

```
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
  1               5                  10                  15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
            20                  25                  30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
        35                  40                  45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
    50                  55                  60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65                  70                  75                  80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
                85                  90                  95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
            100                 105                 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
        115                 120                 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
    130                 135                 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145                 150                 155                 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
                165                 170                 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
            180                 185                 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
        195                 200                 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
    210                 215                 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225                 230                 235                 240
```

```
Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
                245                 250                 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
            260                 265                 270


<210> 157
<211> 300
<212> PRT
<213> Homo sapiens

<400> 157
Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
  1               5                  10                  15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
             20                  25                  30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
         35                  40                  45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
     50                  55                  60

Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
 65                  70                  75                  80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
                85                  90                  95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
            100                 105                 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
        115                 120                 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
    130                 135                 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145                 150                 155                 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
                165                 170                 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
            180                 185                 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
        195                 200                 205

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
    210                 215                 220

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225                 230                 235                 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
                245                 250                 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
            260                 265                 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
        275                 280                 285
```

```
Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
    290                 295                 300


<210> 158
<211> 300
<212> PRT
<213> Homo sapiens

<400> 158
Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
  1               5                  10                  15

Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
            20                  25                  30

Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
        35                  40                  45

Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
    50                  55                  60

Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
65                  70                  75                  80

Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val Leu Cys Gly
                85                  90                  95

Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
            100                 105                 110

Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
        115                 120                 125

His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
    130                 135                 140

Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
145                 150                 155                 160

Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
                165                 170                 175

Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
            180                 185                 190

Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
        195                 200                 205

Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
    210                 215                 220

Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
225                 230                 235                 240

Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
                245                 250                 255

Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
            260                 265                 270

Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
        275                 280                 285

Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
    290                 295                 300
```

<210> 159
<211> 271
<212> PRT
<213> Homo sapiens

<400> 159
Val Ala Glu Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu
1 5 10 15

Arg Leu Val Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro
20 25 30

Cys Arg Arg Asp Ser Pro Thr Thr Cys Gly Pro Cys Pro Pro Arg His
35 40 45

Tyr Thr Gln Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Asn Val
50 55 60

Leu Cys Gly Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His
65 70 75 80

Asn Arg Ala Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe
85 90 95

Cys Leu Glu His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro
100 105 110

Gly Thr Pro Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr
115 120 125

Phe Ser Ala Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn
130 135 140

Cys Thr Ala Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His
145 150 155 160

Asp Thr Leu Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val
165 170 175

Pro Gly Ala Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe
180 185 190

Gln Asp Ile Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu
195 200 205

Ala Pro Glu Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu
210 215 220

Gln Leu Lys Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp
225 230 235 240

Gly Ala Leu Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met
245 250 255

Pro Gly Leu Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
260 265 270

<210> 160
<211> 26
<212> PRT
<213> Homo sapiens

<400> 160
Gly Asp Arg Leu His Cys Lys Pro Gln Arg Gln Ser Pro Trp Met Lys
1 5 10 15

Cys Gln His Leu Asp Pro Glu Gly Gly Gly
20 25

<210> 161
<211> 26
<212> PRT
<213> Homo sapiens

<400> 161
Gly Asp Arg Leu His Cys Lys Pro Gln Arg Gln Ser Pro Trp Met Lys
1 5 10 15

Cys Gln His Leu Asp Pro Glu Gly Gly Gly
20 25

<210> 162
<211> 26
<212> PRT
<213> Homo sapiens

<400> 162
Gly Asp Asp Asp Asp Cys Gly Trp Ile Gly Phe Ala Asn Phe His Leu
1 5 10 15

Cys Leu His Gly Asp Pro Glu Gly Gly Gly
20 25

<210> 163
<211> 26
<212> PRT
<213> Homo sapiens

<400> 163
Gly Asp Asp Asp Asp Cys Gly Trp Ile Gly Phe Ala Asn Phe His Leu
1 5 10 15

Cys Leu His Gly Asp Pro Glu Gly Gly Gly
20 25

<210> 164
<211> 187
<212> PRT
<213> Homo sapiens

<400> 164
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser

```
                85                  90                  95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
            100                 105                 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
        115                 120                 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
    130                 135                 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145                 150                 155                 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
                165                 170                 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
            180                 185


<210> 165
<211> 166
<212> PRT
<213> Homo sapiens

<400> 165
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
  1               5                  10                  15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
            20                  25                  30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
        35                  40                  45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
    50                  55                  60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65                  70                  75                  80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
                85                  90                  95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165


<210> 166
<211> 187
<212> PRT
<213> Homo sapiens

<400> 166
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
```

1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
115 120 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
130 135 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145 150 155 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
180 185

<210> 167
<211> 166
<212> PRT
<213> Homo sapiens

<400> 167
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

```
Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165
```

<210> 168
<211> 167
<212> PRT
<213> Homo sapiens

<400> 168

```
Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu
  1               5                  10                  15

Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys
            20                  25                  30

Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
        35                  40                  45

Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
    50                  55                  60

Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
65                  70                  75                  80

Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
                85                  90                  95

Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
            100                 105                 110

Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
        115                 120                 125

Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
    130                 135                 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
145                 150                 155                 160

Leu Asp Leu Ser Pro Gly Cys
                165
```

<210> 169
<211> 167
<212> PRT
<213> Homo sapiens

<400> 169

```
Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu
  1               5                  10                  15

Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys
            20                  25                  30

Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
        35                  40                  45

Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
    50                  55                  60

Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
65                  70                  75                  80
```

Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
85 90 95

Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
100 105 110

Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
115 120 125

Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
130 135 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
145 150 155 160

Leu Asp Leu Ser Pro Gly Cys
165

<210> 170
<211> 167
<212> PRT
<213> Homo sapiens

<400> 170
Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu
1 5 10 15

Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys
20 25 30

Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
35 40 45

Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
50 55 60

Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
65 70 75 80

Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
85 90 95

Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
100 105 110

Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
115 120 125

Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
130 135 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
145 150 155 160

Leu Asp Leu Ser Pro Gly Cys
165

<210> 171
<211> 167
<212> PRT
<213> Homo sapiens

<400> 171
Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr Leu

```
1               5                  10                  15

Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp Thr Lys
            20                  25                  30

Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile Ser His Thr
        35                  40                  45

Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu Asp Phe Ile Pro
    50                  55                  60

Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met Asp Gln Thr Leu Ala
65                  70                  75                  80

Val Tyr Gln Gln Ile Leu Thr Ser Met Pro Ser Arg Asn Val Ile Gln
                85                  90                  95

Ile Ser Asn Asp Leu Glu Asn Leu Arg Asp Leu Leu His Val Leu Ala
            100                 105                 110

Phe Ser Lys Ser Cys His Leu Pro Trp Ala Ser Gly Leu Glu Thr Leu
        115                 120                 125

Asp Ser Leu Gly Gly Val Leu Glu Ala Ser Gly Tyr Ser Thr Glu Val
    130                 135                 140

Val Ala Leu Ser Arg Leu Gln Gly Ser Leu Gln Asp Met Leu Trp Gln
145                 150                 155                 160

Leu Asp Leu Ser Pro Gly Cys
                165
```

<210> 172
<211> 165
<212> PRT
<213> Homo sapiens

<400> 172

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
  1               5                  10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
```

Leu Arg Ser Lys Glu
165

<210> 173
<211> 63
<212> PRT
<213> Homo sapiens

<400> 173
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 174
<211> 63
<212> PRT
<213> Homo sapiens

<400> 174
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 175
<211> 58
<212> PRT
<213> Homo sapiens

<400> 175
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Gly
20 25 30

Gly Pro Gly Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55

<210> 176
<211> 58
<212> PRT
<213> Homo sapiens

<400> 176
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Gly
20 25 30

Gly Pro Gly Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55

<210> 177
<211> 108
<212> PRT
<213> Homo sapiens

<400> 177
Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val
1 5 10 15

Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
20 25 30

Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
35 40 45

Leu Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
50 55 60

Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
65 70 75 80

Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
85 90 95

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
100 105

<210> 178
<211> 108
<212> PRT
<213> Homo sapiens

<400> 178
Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val
1 5 10 15

Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
20 25 30

Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
35 40 45

Leu Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
50 55 60

Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
65 70 75 80

Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
85 90 95

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
100 105

<210> 179
<211> 108
<212> PRT
<213> Homo sapiens

<400> 179
Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val
1 5 10 15

Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
20 25 30

Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
35 40 45

Leu Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
50 55 60

Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
65 70 75 80

Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
85 90 95

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
100 105

<210> 180
<211> 108
<212> PRT
<213> Homo sapiens

<400> 180
Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val
1 5 10 15

Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
20 25 30

Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
35 40 45

Leu Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
50 55 60

Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
65 70 75 80

Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
85 90 95

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
100 105

<210> 181
<211> 108
<212> PRT
<213> Homo sapiens

<400> 181
Met Lys Ala Leu Cys Leu Leu Leu Leu Pro Val Leu Gly Leu Leu Val
1 5 10 15

```
Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile Asn Glu Arg Ile
            20                  25                  30

Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile Ser Ser Ile Gly
        35                  40                  45

Leu Glu Cys Gln Ser Val Thr Ser Arg Gly Asp Leu Ala Thr Cys Pro
    50                  55                  60

Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser Ala Cys Gly Ser
65                  70                  75                  80

Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln Cys Ala Gly Met
                85                  90                  95

Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
            100                 105
```

<210> 182
<211> 429
<212> PRT
<213> Homo sapiens

<400> 182

```
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
            20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
    50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220
```

```
Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425
```

<210> 183
<211> 429
<212> PRT
<213> Homo sapiens

<400> 183

```
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
             20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
         35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
     50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
 65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                 85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
```

```
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425
```

<210> 184
<211> 165
<212> PRT
<213> Homo sapiens

<400> 184
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met

```
  1               5                  10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> 185
<211> 429
<212> PRT
<213> Homo sapiens

<400> 185
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
            20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
    50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160
```

```
Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425
```

<210> 186
<211> 429
<212> PRT
<213> Homo sapiens

<400> 186

```
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
            20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45
```

```
Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
     50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
 65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                 85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415
```

```
His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
          420                 425


<210> 187
<211> 429
<212> PRT
<213> Homo sapiens

<400> 187
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
             20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
         35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
     50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
 65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                 85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300
```

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305 310 315 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
325 330 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
340 345 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
355 360 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
370 375 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385 390 395 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
420 425

<210> 188
<211> 429
<212> PRT
<213> Homo sapiens

<400> 188
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
1 5 10 15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
20 25 30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
35 40 45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
50 55 60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65 70 75 80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
85 90 95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
100 105 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
115 120 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
130 135 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145 150 155 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
165 170 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
180 185 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser

195 200 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
210 215 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225 230 235 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
245 250 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
260 265 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
275 280 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
290 295 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305 310 315 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
325 330 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
340 345 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
355 360 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
370 375 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385 390 395 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
420 425

<210> 189
<211> 165
<212> PRT
<213> Homo sapiens

<400> 189
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

```
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165
```

<210> 190
<211> 429
<212> PRT
<213> Homo sapiens

<400> 190

```
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
            20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
    50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240
```

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
245 250 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
260 265 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
275 280 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
290 295 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305 310 315 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
325 330 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
340 345 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
355 360 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
370 375 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385 390 395 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
420 425

<210> 191
<211> 429
<212> PRT
<213> Homo sapiens

<400> 191
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
1 5 10 15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
20 25 30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
35 40 45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
50 55 60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65 70 75 80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
85 90 95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
100 105 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
115 120 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
130 135 140

```
Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425
```

<210> 192
<211> 429
<212> PRT
<213> Homo sapiens

<400> 192

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Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
```

```
            20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
    50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380
```

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385 390 395 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
420 425

<210> 193
<211> 165
<212> PRT
<213> Homo sapiens

<400> 193
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 194
<211> 165
<212> PRT
<213> Homo sapiens

<400> 194
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

```
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165
```

<210> 195
<211> 346
<212> PRT
<213> Homo sapiens

<400> 195

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Met Asp Pro Ala Arg Lys Ala Gly Ala Gln Ala Met Ile Trp Thr Ala
  1               5                  10                  15

Gly Trp Leu Leu Leu Leu Leu Leu Arg Gly Gly Ala Gln Ala Leu Glu
            20                  25                  30

Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro Asn Lys
        35                  40                  45

Met Lys Thr Val Lys Cys Ala Pro Gly Val Asp Val Cys Thr Glu Ala
    50                  55                  60

Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Leu Ala Val Arg
65                  70                  75                  80

Gly Cys Gly Ser Gly Leu Pro Gly Lys Asn Asp Arg Gly Leu Asp Leu
                85                  90                  95

His Gly Leu Leu Ala Phe Ile Gln Leu Gln Gln Cys Ala Gln Asp Arg
            100                 105                 110

Cys Asn Ala Lys Leu Asn Leu Thr Ser Arg Ala Leu Asp Pro Ala Gly
        115                 120                 125

Asn Glu Ser Ala Tyr Pro Pro Asn Gly Val Glu Cys Tyr Ser Cys Val
    130                 135                 140

Gly Leu Ser Arg Glu Ala Cys Gln Gly Thr Ser Pro Pro Val Val Ser
145                 150                 155                 160

Cys Tyr Asn Ala Ser Asp His Val Tyr Lys Gly Cys Phe Asp Gly Asn
                165                 170                 175

Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val Arg Gly
            180                 185                 190

Cys Val Gln Asp Glu Phe Cys Thr Arg Asp Gly Val Thr Gly Pro Gly
        195                 200                 205
```

```
Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Ser Arg Cys Asn Ser Asp
    210                 215                 220

Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu Val Arg
225                 230                 235                 240

Leu Pro Pro Pro Glu Pro Thr Thr Val Ala Ser Thr Thr Ser Val Thr
                245                 250                 255

Thr Ser Thr Ser Ala Pro Val Arg Pro Thr Ser Thr Thr Lys Pro Met
            260                 265                 270

Pro Ala Pro Thr Ser Gln Thr Pro Arg Gln Gly Val Glu His Glu Ala
        275                 280                 285

Ser Arg Asp Glu Glu Pro Arg Leu Thr Gly Gly Ala Ala Gly His Gln
    290                 295                 300

Asp Arg Ser Asn Ser Gly Gln Tyr Pro Ala Lys Gly Gly Pro Gln Gln
305                 310                 315                 320

Pro His Asn Lys Gly Cys Val Ala Pro Thr Ala Gly Leu Ala Ala Leu
                325                 330                 335

Leu Leu Ala Val Ala Ala Gly Val Leu Leu
            340                 345
```

<210> 196
<211> 346
<212> PRT
<213> Homo sapiens

<400> 196

```
Met Asp Pro Ala Arg Lys Ala Gly Ala Gln Ala Met Ile Trp Thr Ala
  1               5                  10                  15

Gly Trp Leu Leu Leu Leu Leu Leu Arg Gly Gly Ala Gln Ala Leu Glu
            20                  25                  30

Cys Tyr Ser Cys Val Gln Lys Ala Asp Asp Gly Cys Ser Pro Asn Lys
        35                  40                  45

Met Lys Thr Val Lys Cys Ala Pro Gly Val Asp Val Cys Thr Glu Ala
    50                  55                  60

Val Gly Ala Val Glu Thr Ile His Gly Gln Phe Ser Leu Ala Val Arg
65                  70                  75                  80

Gly Cys Gly Ser Gly Leu Pro Gly Lys Asn Asp Arg Gly Leu Asp Leu
                85                  90                  95

His Gly Leu Leu Ala Phe Ile Gln Leu Gln Gln Cys Ala Gln Asp Arg
            100                 105                 110

Cys Asn Ala Lys Leu Asn Leu Thr Ser Arg Ala Leu Asp Pro Ala Gly
        115                 120                 125

Asn Glu Ser Ala Tyr Pro Pro Asn Gly Val Glu Cys Tyr Ser Cys Val
    130                 135                 140

Gly Leu Ser Arg Glu Ala Cys Gln Gly Thr Ser Pro Pro Val Val Ser
145                 150                 155                 160

Cys Tyr Asn Ala Ser Asp His Val Tyr Lys Gly Cys Phe Asp Gly Asn
```

165 170 175

Val Thr Leu Thr Ala Ala Asn Val Thr Val Ser Leu Pro Val Arg Gly
180 185 190

Cys Val Gln Asp Glu Phe Cys Thr Arg Asp Gly Val Thr Gly Pro Gly
195 200 205

Phe Thr Leu Ser Gly Ser Cys Cys Gln Gly Ser Arg Cys Asn Ser Asp
210 215 220

Leu Arg Asn Lys Thr Tyr Phe Ser Pro Arg Ile Pro Pro Leu Val Arg
225 230 235 240

Leu Pro Pro Pro Glu Pro Thr Thr Val Ala Ser Thr Thr Ser Val Thr
245 250 255

Thr Ser Thr Ser Ala Pro Val Arg Pro Thr Ser Thr Thr Lys Pro Met
260 265 270

Pro Ala Pro Thr Ser Gln Thr Pro Arg Gln Gly Val Glu His Glu Ala
275 280 285

Ser Arg Asp Glu Glu Pro Arg Leu Thr Gly Gly Ala Ala Gly His Gln
290 295 300

Asp Arg Ser Asn Ser Gly Gln Tyr Pro Ala Lys Gly Gly Pro Gln Gln
305 310 315 320

Pro His Asn Lys Gly Cys Val Ala Pro Thr Ala Gly Leu Ala Ala Leu
325 330 335

Leu Leu Ala Val Ala Ala Gly Val Leu Leu
340 345

<210> 197
<211> 165
<212> PRT
<213> Homo sapiens

<400> 197
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 198
<211> 180
<212> PRT
<213> Homo sapiens

<400> 198
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 199
<211> 180
<212> PRT
<213> Homo sapiens

<400> 199
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys

50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 200
<211> 180
<212> PRT
<213> Homo sapiens

<400> 200
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 201
<211> 180
<212> PRT
<213> Homo sapiens

<400> 201
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 202
<211> 87
<212> PRT
<213> Homo sapiens

<400> 202
Met Lys Ile Ile Leu Trp Leu Cys Val Phe Gly Leu Phe Leu Ala Thr
1 5 10 15

Leu Phe Pro Ile Ser Trp Gln Met Pro Val Glu Ser Gly Leu Ser Ser
20 25 30

Glu Asp Ser Ala Ser Ser Glu Ser Phe Ala Ser Lys Ile Lys Arg His
35 40 45

Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu
50 55 60

Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser
65 70 75 80

Gly Ala Pro Pro Pro Ser Gly
85

<210> 203
<211> 87
<212> PRT
<213> Homo sapiens

<400> 203
Met Lys Ile Ile Leu Trp Leu Cys Val Phe Gly Leu Phe Leu Ala Thr
1 5 10 15

Leu Phe Pro Ile Ser Trp Gln Met Pro Val Glu Ser Gly Leu Ser Ser
20 25 30

Glu Asp Ser Ala Ser Ser Glu Ser Phe Ala Ser Lys Ile Lys Arg His
35 40 45

Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu
50 55 60

Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser
65 70 75 80

Gly Ala Pro Pro Pro Ser Gly
85

<210> 204
<211> 110
<212> PRT
<213> Homo sapiens

<400> 204
Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn
1 5 10 15

Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr
20 25 30

Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp
35 40 45

Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys
50 55 60

Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser
65 70 75 80

Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys
85 90 95

Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
100 105 110

<210> 205
<211> 136
<212> PRT
<213> Homo sapiens

<400> 205
Met Arg Thr Pro Gly Pro Leu Pro Val Leu Leu Leu Leu Leu Ala Gly
1 5 10 15

Ala Pro Ala Ala Arg Pro Thr Pro Pro Thr Cys Tyr Ser Arg Met Arg
20 25 30

Ala Leu Ser Gln Glu Ile Thr Arg Asp Phe Asn Leu Leu Gln Val Ser

35 40 45

Glu Pro Ser Glu Pro Cys Val Arg Tyr Leu Pro Arg Leu Tyr Leu Asp
50 55 60

Ile His Asn Tyr Cys Val Leu Asp Lys Leu Arg Asp Phe Val Ala Ser
65 70 75 80

Pro Pro Cys Trp Lys Val Ala Gln Val Asp Ser Leu Lys Asp Lys Ala
85 90 95

Arg Lys Leu Tyr Thr Ile Met Asn Ser Phe Cys Arg Arg Asp Leu Val
100 105 110

Phe Leu Leu Asp Asp Cys Asn Ala Leu Glu Tyr Pro Ile Pro Val Thr
115 120 125

Thr Val Leu Pro Asp Arg Gln Arg
130 135

<210> 206
<211> 136
<212> PRT
<213> Homo sapiens

<400> 206
Met Arg Thr Pro Gly Pro Leu Pro Val Leu Leu Leu Leu Leu Ala Gly
1 5 10 15

Ala Pro Ala Ala Arg Pro Thr Pro Pro Thr Cys Tyr Ser Arg Met Arg
20 25 30

Ala Leu Ser Gln Glu Ile Thr Arg Asp Phe Asn Leu Leu Gln Val Ser
35 40 45

Glu Pro Ser Glu Pro Cys Val Arg Tyr Leu Pro Arg Leu Tyr Leu Asp
50 55 60

Ile His Asn Tyr Cys Val Leu Asp Lys Leu Arg Asp Phe Val Ala Ser
65 70 75 80

Pro Pro Cys Trp Lys Val Ala Gln Val Asp Ser Leu Lys Asp Lys Ala
85 90 95

Arg Lys Leu Tyr Thr Ile Met Asn Ser Phe Cys Arg Arg Asp Leu Val
100 105 110

Phe Leu Leu Asp Asp Cys Asn Ala Leu Glu Tyr Pro Ile Pro Val Thr
115 120 125

Thr Val Leu Pro Asp Arg Gln Arg
130 135

<210> 207
<211> 187
<212> PRT
<213> Homo sapiens

<400> 207
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
115 120 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
130 135 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145 150 155 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
180 185

<210> 208
<211> 44
<212> DNA
<213> Homo sapiens

<400> 208
gagcgcggat ccgccttagg cgtggcagaa acacccacct accc 44

<210> 209
<211> 38
<212> DNA
<213> Homo sapiens

<400> 209
cggtgcgcgg ccgcttagtg cacagggagg aagcgctc 38

<210> 210
<211> 27
<212> DNA
<213> Homo sapiens

<400> 210
ggccggctcg aggttgctga aacacca 27

<210> 211
<211> 53
<212> DNA
<213> Homo sapiens

<400> 211
gcgcgcgcgg ccgcttattc tctaacagat ctttccaaac caggcattct agc 53

<210> 212
<211> 27
<212> DNA
<213> Homo sapiens

<400> 212
ggccggctcg aggttgctga aacacca 27

<210> 213
<211> 35
<212> DNA
<213> Homo sapiens

<400> 213
gcgcgcgcgg ccgcttacaa accaggcatt ctagc 35

<210> 214
<211> 27
<212> DNA
<213> Homo sapiens

<400> 214
ggccggctcg aggttgctga aacacca 27

<210> 215
<211> 37
<212> DNA
<213> Homo sapiens

<400> 215
gcgcgcgcgc ggccgcttat ctagcaactc tcaaagc 37

<210> 216
<211> 38
<212> DNA
<213> Homo sapiens

<400> 216
gctagtcctt aggcttagtt gctgaaacac caacttac 38

<210> 217
<211> 37
<212> DNA
<213> Homo sapiens

<400> 217
gtcagcctcg agcggccgcg atccgtgtgg aagaacg 37

<210> 218
<211> 89
<212> DNA
<213> Homo sapiens

<400> 218
cgtagcaagc tttatttccc ttctttttct ctttagctcg gcttattcca ggagcttgga 60
taaaagagtt gctgaaacac caacttacc 89

<210> 219
<211> 23
<212> DNA
<213> Homo sapiens

<400> 219
gcttattata agcctaaggc agc 23

<210> 220
<211> 32
<212> DNA
<213> Homo sapiens

<400> 220
ggatccgcca tcatgagggc gctggagggg cc 32

<210> 221
<211> 41
<212> DNA
<213> Homo sapiens

<400> 221
gtcgtcggta ccttataagc ctaaggcagc ttgacttgca g 41

<210> 222
<211> 50
<212> DNA
<213> Homo sapiens

<400> 222
gactggatcc gccatcatga agtgggtaac ctttatttcc cttcttttc 50

<210> 223
<211> 45
<212> DNA
<213> Homo sapiens

<400> 223
cggtgccggt gcgcggccgc ttagtgcaca ggcaggaagc gttcc 45

<210> 224
<211> 39
<212> DNA
<213> Homo sapiens

<400> 224
gaacaatgtc aaccacatag acaatgtact gctttgggt 39

<210> 225
<211> 21
<212> DNA
<213> Homo sapiens

<400> 225
gatagtcttc tgcacagggc a 21

<210> 226
<211> 38
<212> DNA
<213> Homo sapiens

<400> 226
gctagtcctt aggcttagtt gctgaaacac caacttac 38

<210> 227
<211> 36
<212> DNA
<213> Homo sapiens

<400> 227
ggggtacctt attagtgaac tggcaaaaat ctttct 36

<210> 228
<211> 42
<212> DNA
<213> Homo sapiens

<400> 228
ggccggctcg aggatgacga tgacaagctg gattgcaacc tg 42

<210> 229

<211> 35
<212> DNA
<213> Homo sapiens

<400> 229
gcgcgcgcgg ccgcttacaa accaggcatt ctagc 35

<210> 230
<211> 42
<212> DNA
<213> Homo sapiens

<400> 230
ggccggctcg aggatgacga tgacaagctg gattgcaacc tg 42

<210> 231
<211> 37
<212> DNA
<213> Homo sapiens

<400> 231
gcgcgcgcgc ggccgcttat ctagcaactc tcaaagc 37

<210> 232
<211> 27
<212> DNA
<213> Homo sapiens

<400> 232
ggccggctcg aggttgctga aacacca 27

<210> 233
<211> 35
<212> DNA
<213> Homo sapiens

<400> 233
gcgcgcgcgg ccgcttactc acggacgctc cgctc 35

<210> 234
<211> 41
<212> DNA
<213> Homo sapiens

<400> 234
aggagcgtcg acaaaagatt gcccgcccag gtggcattta c 41

<210> 235
<211> 57
<212> DNA
<213> Homo sapiens

<400> 235
ctttaaatcg atgagcaacc tcactcttgt gtgcatcgtc gccagtgctc ccttcag 57

<210> 236
<211> 40
<212> DNA
<213> Homo sapiens

<400> 236
cgcgcgcgtc gacaaaagaa tgagctacaa cttgcttgga 40

<210> 237
<211> 55
<212> DNA
<213> Homo sapiens

<400> 237
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcgtt tcggaggtaa cctgt 55

<210> 238
<211> 40
<212> DNA
<213> Homo sapiens

<400> 238
aagctgcctt aggcttattg cccgcccagg tggcatttac 40

<210> 239
<211> 43
<212> DNA
<213> Homo sapiens

<400> 239
gcgcgcggcc ggccggtacc ttagtcgcca gtgctccctt cag 43

<210> 240
<211> 38
<212> DNA
<213> Homo sapiens

<400> 240
atgacgcccg gggccaccat gaagtgggta acctttat 38

<210> 241
<211> 32
<212> DNA
<213> Homo sapiens

<400> 241
gcctatgaat tcttagtgca caggcaggaa gc 32

<210> 242
<211> 40
<212> DNA
<213> Homo sapiens

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<211> 69
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tggatgaag 69

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<211> 91
<212> DNA
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gttgacactt catccatgga gattgtcttt g 91

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acttgtg 67

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gcgaaacc 68

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acttg 65

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gcgaaaccaa tc 72

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tgtgcttctc cactacagct ctttccatga gctacaactt gcttgg 106

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<213> Homo sapiens

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<212> DNA
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<212> DNA
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ctttgtactt ggtttgtggt gaa 83

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<212> DNA
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gaagtacaa 69

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<211> 84
<212> DNA
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gctttgtact tggtttgtgg tgaa 84

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ggtacaaaga acaaatagaa gtacaa 86

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ctttgtactt ggtttgtggt gaa 83

<210> 274
<211> 69
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gaagtacaa 69

<210> 275
<211> 84
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gctttgtact tggtttgtgg tgaa 84

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<400> 276

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ggtacaaaga acaaatagaa gtacaa 86

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<400> 277
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<210> 278
<211> 60
<212> DNA
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<400> 278
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<210> 281
<211> 40
<212> DNA
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<400> 281
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<210> 282
<211> 66
<212> DNA
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agcgcg 66

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<210> 287
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<212> DNA
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<212> DNA
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<400> 289
gcgcgggtac cttactacct gcacccacac tctg 34

<210> 290
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<212> DNA
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<400> 290
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<210> 291
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<212> DNA
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ttactgccct tggatcccag gccagcgccg gggctggcag ccac 104

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<212> DNA
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<400> 293
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<210> 294
<211> 32
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<400> 294
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<210> 295
<211> 34
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<400> 295
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<210> 296
<211> 41
<212> DNA
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<400> 296
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<210> 297
<211> 59
<212> DNA
<213> Homo sapiens

<400> 297
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<400> 298
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cttgttactg cccttggatc ccaggccagc gccggggctg gcagccac 108

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<211> 60
<212> DNA
<213> Homo sapiens

<400> 299
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<211> 45
<212> DNA
<213> Homo sapiens

<400> 300
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<211> 62
<212> DNA
<213> Homo sapiens

<400> 301
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tc 62

<210> 302
<211> 38
<212> DNA
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<400> 302
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<210> 303
<211> 39
<212> DNA
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<400> 303
gaattcggcg cgccttattc cttacttctt aaactttct 39

<210> 304
<211> 107
<212> DNA
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<400> 304
gcgcgcggat ccgccaccat ggccttgacc tttgctttac tggtggccct cctggtgctc 60
agctgcaagt caagctgctc tgtgggctgt gatctgcctc aaaccca 107

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<400> 306
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<210> 307
<211> 57
<212> DNA
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<400> 307
agtcccatcg atgagcaacc tcactcttgt gtgcatcatt atggggctgc tggggcc 57

<210> 308
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<400> 308
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<210> 309
<211> 57

<212> DNA
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<400> 309
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<210> 310
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<212> DNA
<213> Homo sapiens

<400> 310
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<210> 311
<211> 59
<212> DNA
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<400> 311
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<210> 314
<211> 89
<212> DNA
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<400> 314
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aaggtcaagc tgctaaggaa ttcattgct 89

<210> 315
<211> 49
<212> DNA
<213> Homo sapiens

<400> 315
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<210> 316
<211> 90
<212> DNA
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gaaggtcaag ctgctaagga attcattgct 90

<210> 317
<211> 75
<212> DNA
<213> Homo sapiens

<400> 317
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tgaattcctt agcag 75

<210> 318
<211> 89
<212> DNA
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aaggtcaagc tgctaaggaa ttcattgct 89

<210> 319
<211> 49
<212> DNA
<213> Homo sapiens

<400> 319
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<210> 320
<211> 33
<212> DNA
<213> Homo sapiens

<400> 320
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<210> 321
<211> 32
<212> DNA
<213> Homo sapiens

<400> 321
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<210> 322
<211> 37
<212> DNA
<213> Homo sapiens

<400> 322
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<210> 323
<211> 44
<212> DNA
<213> Homo sapiens

<400> 323
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<210> 324
<211> 38
<212> DNA
<213> Homo sapiens

<400> 324
aggagcgtcg acaaaagagc gcggcccact cccccgac 38

<210> 325

<211> 58
<212> DNA
<213> Homo sapiens

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<210> 326
<211> 1782
<212> DNA
<213> Homo sapiens

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aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240
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gccaagtata tctgtgaaaa tcaggattcg atctccagta aactgaagga atgctgtgaa 840
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<212> PRT
<213> Homo Sapiens

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro

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                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445
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Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
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<211> 58
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<220>
<221> primer_bind
<223> primer used to generate XhoI and ClaI site in pPPC0006

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gcctcgagaa aagagatgca cacaagagtg aggttgctca tcgatttaaa gatttggg 58

<210> 329
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<212> DNA
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<220>
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<223> primer used in generation XhoI and ClaI site in pPPC0006

<400> 329
aatcgatgag caacctcact cttgtgtgca tctcttttct cgaggctcct ggaataagc 59

<210> 330
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<212> DNA
<213> Artificial Sequence

<220>
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<400> 330

tacaaactta agagtccaat tagc 24

<210> 331
<211> 29
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<220>
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<223> primer used in generation XhoI and ClaI
site in pPPC0006

<400> 331
cacttctcta gagtggtttc atatgtctt 29

<210> 332
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> Misc_Structure
<223> Synthetic oligonucleotide used to alter restriction
sites in pPPC0007

<400> 332
aagctgcctt aggcttataa taaggcgcgc cggccggccg tttaaactaa gcttaattct 60

<210> 333
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<221> Misc_Structure
<223> Synthetic oligonucleotide used to alter restriction
sites in pPPC0007

<400> 333
agaattaagc ttagtttaaa cggccggccg gcgcgcctta ttataagcct aaggcagctt 60

<210> 334
<211> 32
<212> DNA
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<220>
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<223> forward primer useful for generation of albumin
fusion protein in which the albumin moiety is N-terminal
of the Therapeutic Protein

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<400> 334
aagctgcctt aggcttannn nnnnnnnnnn nn 32

<210> 335
<211> 51

<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> reverse primer useful for generation of albumin fusion protein in which the albumin moiety is N-terminal of the Therapeutic Protein

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<222> (37)
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<223> n equals a,t,g, or c

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<222> (51)
<223> n equals a,t,g, or c

<400> 335
gcgcgcgttt aaacggccgg ccggcgcgcc ttattannnn nnnnnnnnnn n 51

<210> 336
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> forward primer useful for generation of albumin fusion protein in which the albumin moiety is c-terminal of the Therapeutic Protein

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<221> misc_feature
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<400> 336
aggagcgtcg acaaaagann nnnnnnnnnn nnn 33

<210> 337
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> reverse primer useful for generation of albumin fusion protein in which the albumin moiety is c-terminal of the Therapeutic Protein

<220>
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<220>
<221> misc_feature
<222> (52)
<223> n equals a,t,g, or c

<400> 337
ctttaaatcg atgagcaacc tcactcttgt gtgcatcnnn nnnnnnnnnn nn 52

<210> 338
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> forward primer useful for inserting Therapeutic protein into pC4:HSA vector

<220>
<221> misc_feature
<222> (29)
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<220>
<221> misc_feature
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<400> 338
ccgccgctcg aggggtgtgt ttcgtcgann nnnnnnnnnn nnnnnn 46

<210> 339
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> reverse primer useful for inserting Therapeutic protein into pC4:HSA vector

<220>
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<223> n equals a,t,g, or c

<220>
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<222> (43)
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<400> 339
agtcccatcg atgagcaacc tcactcttgt gtgcatcnnn nnnnnnnnnn nnnnn 55

<210> 340
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<221> signal
<223> Stanniocalcin signal peptide

<400> 340
Met Leu Gln Asn Ser Ala Val Leu Leu Leu Leu Val Ile Ser Ala Ser
1 5 10 15

Ala

<210> 341
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> signal
<223> Synthetic signal peptide

<400> 341
Met Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala Leu
1 5 10 15

Trp Ala Pro Ala Arg Gly
20

<210> 342
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate VH forward primer useful for
amplifying human VH domains

<400> 342
caggtgcagc tggtgcagtc tgg 23

<210> 343
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate VH forward primer useful for
amplifying human VH domains

<400> 343
caggtcaact taagggagtc tgg 23

<210> 344
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate VH forward primer useful for
amplifying human VH domains

<400> 344
gaggtgcagc tggtggagtc tgg 23

<210> 345
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 345
caggtgcagc tgcaggagtc ggg 23

<210> 346
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 346
gaggtgcagc tgttgcagtc tgc 23

<210> 347
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 347
caggtacagc tgcagcagtc agg 23

<210> 348
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 348
tgaggagacg gtgaccaggg tgcc 24

<210> 349
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 349
tgaagagacg gtgaccattg tccc 24

<210> 350
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 350
tgaggagacg gtgaccaggg ttcc 24

<210> 351
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 351
tgaggagacg gtgaccgtgg tccc 24

<210> 352
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 352
gacatccaga tgacccagtc tcc 23

<210> 353
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 353
gatgttgtga tgactcagtc tcc 23

<210> 354
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 354
gatattgtga tgactcagtc tcc 23

<210> 355
<211> 23
<212> DNA

<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 355
gaaattgtgt tgacgcagtc tcc 23

<210> 356
<211> 23
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<220>
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<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 356
gacatcgtga tgacccagtc tcc 23

<210> 357
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 357
gaaacgacac tcacgcagtc tcc 23

<210> 358
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 358
gaaattgtgc tgactcagtc tcc 23

<210> 359
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 359
cagtctgtgt tgacgcagcc gcc 23

<210> 360
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<221> primer_bind
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 360
cagtctgccc tgactcagcc tgc 23

<210> 361
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 361
tcctatgtgc tgactcagcc acc 23

<210> 362
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
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<400> 362
tcttctgagc tgactcagga ccc 23

<210> 363
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 363
cacgttatac tgactcaacc gcc 23

<210> 364
<211> 23
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<213> Artificial Sequence

<220>
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<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 364
caggctgtgc tcactcagcc gtc 23

<210> 365
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 365
aattttatgc tgactcagcc cca 23

<210> 366
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 366
acgtttgatt tccaccttgg tccc 24

<210> 367
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 367
acgtttgatc tccagcttgg tccc 24

<210> 368
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 368
acgtttgata tccactttgg tccc 24

<210> 369
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 369
acgtttgatc tccaccttgg tccc 24

<210> 370
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 370
acgtttaatc tccagtcgtg tccc 24

<210> 371
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 371
cagtctgtgt tgacgcagcc gcc 23

<210> 372
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 372
cagtctgccc tgactcagcc tgc 23

<210> 373
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 373
tcctatgtgc tgactcagcc acc 23

<210> 374
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 374
tcttctgagc tgactcagga ccc 23

<210> 375
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 375
cacgttatac tgactcaacc gcc 23

<210> 376
<211> 23

<212> DNA
<213> Artificial Sequence

<220>
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<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 376
caggctgtgc tcactcagcc gtc 23

<210> 377
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> primer_bind
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 377
aattttatgc tgactcagcc cca 23

<210> 378
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> turn
<223> Linker peptide that may be used to join VH and VL domains in an scFv.

<400> 378
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 379
<211> 609
<212> PRT
<213> Homo sapiens

<400> 379
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln

115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

```
Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu
```

<210> 380
<211> 19
<212> PRT
<213> Homo sapiens

<400> 380
```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
  1               5                  10                  15

Val His Ser
```

<210> 381
<211> 29
<212> PRT
<213> Homo sapiens

<400> 381
```
Met Glu Arg Ala Ala Pro Ser Arg Arg Val Pro Leu Pro Leu Leu Leu
  1               5                  10                  15

Leu Gly Gly Leu Ala Leu Leu Ala Ala Gly Val Asp Ala
            20                  25
```

<210> 382
<211> 22
<212> PRT
<213> Homo sapiens

<400> 382
```
Met Met Lys Thr Leu Leu Leu Phe Val Gly Leu Leu Leu Thr Trp Glu
  1               5                  10                  15

Ser Gly Gln Val Leu Gly
            20
```

<210> 383
<211> 21
<212> PRT
<213> Homo sapiens

<400> 383
Met Leu Pro Leu Cys Leu Val Ala Ala Leu Leu Leu Ala Ala Gly Pro
1 5 10 15

Gly Pro Ser Leu Gly
20

<210> 384
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 384
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
1 5 10 15

Leu Gly

<210> 385
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 385
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
1 5 10 15

Leu Gly

<210> 386
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 386
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Leu Gly

<210> 387
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)

<223> Variant of HSA native leader

<400> 387
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
1 5 10 15

Ser Gly

<210> 388
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 388
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
1 5 10 15

Ser Gly

<210> 389
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (18)
<223> Variant of HSA native leader

<400> 389
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Ser Gly

<210> 390
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> MUTAGEN
<222> (14) to (23)
<223> Variant of HSA native leader

<400> 390
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Leu Gly Asp Leu His Lys Ser
20

<210> 391
<211> 9
<212> PRT
<213> Homo sapiens

<400> 391
Asp Ala His Lys Ser Glu Val Ala His
1 5

<210> 392
<211> 11
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<222> (1) to (11)
<223> Kozak sequence

<400> 392
ccgccaccat g 11

<210> 393
<211> 19
<212> PRT
<213> Homo sapiens

<400> 393
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala

<210> 394
<211> 86
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (84)
<223> Xaa equals any one of Glu or Asp

<400> 394
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Ala Phe Ala Ala Ser
1 5 10 15

Ser Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala
20 25 30

Gln Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp
35 40 45

Phe Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu
50 55 60

Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly
65 70 75 80

Val Ser Leu Xaa Lys Arg
85

<210> 395
<211> 24
<212> PRT
<213> Homo sapiens

<400> 395
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Glu Lys Arg
20

<210> 396

<211> 24
<212> PRT
<213> Homo sapiens

<400> 396
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg
20

<210> 397
<211> 733
<212> DNA
<213> Homo sapiens

<400> 397
gggatccgga gcccaaatct tctgacaaaa ctcacacatg cccaccgtgc ccagcacctg 60
aattcgaggg tgcaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 120
tctcccggac tcctgaggtc acatgcgtgg tggtggacgt aagccacgaa gaccctgagg 180
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 240
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 300
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca acccccatcg 360
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 420
catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 480
atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 540
ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag ctcaccgtgg 600
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 660
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgagtg cgacggccgc 720
gactctagag gat 733

<210> 398
<211> 5
<212> PRT
<213> Homo sapiens

<220>
<221> Site
<222> (3)
<223> Xaa equals any of the twenty naturally ocurring L-amino acids

<400> 398
Trp Ser Xaa Trp Ser
1 5

<210> 399
<211> 86
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic sequence with 4 tandem copies of the GAS binding site found in the IRF1 promoter (Rothman et al., Immunity 1:457-468 (1994)), 18 nucleotides complementary to the SV40 early promoter, and a Xho I restriction site.

<400> 399
gcgcctcgag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc 60
cccgaaatat ctgccatctc aattag 86

<210> 400
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind

<223> Synthetic sequence complementary to the SV40 promter; includes a Hind III restriction site.

<400> 400
gcggcaagct ttttgcaaag cctaggc 27

<210> 401
<211> 271
<212> DNA
<213> Artificial Sequence

<220>
<221> Protein_Bind
<223> Synthetic promoter for use in biological assays; includes GAS binding sites found in the IRF1 promoter (Rothman et al., Immunity 1:457-468 (1994)).

<400> 401
ctcgagattt ccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg 60
aaatatctgc catctcaatt agtcagcaac catagtcccg cccctaactc cgcccatccc 120
gcccctaact ccgcccagtt ccgcccattc tccgccccat ggctgactaa ttttttttat 180
ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt 240
ttttggaggc ctaggctttt gcaaaaagct t 271

<210> 402
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence (Sakamoto et al., Oncogene 6:867-871 (1991)); includes a Xho I restriction site.

<400> 402
gcgctcgagg gatgacagcg atagaacccc gg 32

<210> 403
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence (Sakamoto et al., Oncogene 6:867-871 (1991)); includes a Hind III restriction site.

<400> 403
gcgaagcttc gcgactcccc ggatccgcct c 31

<210> 404
<211> 12
<212> DNA
<213> Homo sapiens

<400> 404
ggggactttc cc 12

<210> 405
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic primer with 4 tandem copies of the NF-KB binding site

(GGGGACTTTCCC), 18 nucleotides complementary to the 5' end of the SV40 early promoter sequence, and a XhoI restriction site.

<400> 405
gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg 60
ccatctcaat tag 73

<210> 406
<211> 256
<212> DNA
<213> Artificial Sequence

<220>
<221> Protein_Bind
<223> Synthetic promoter for use in biological assays; includes NF-KB binding sites.

<400> 406
ctcgagggga ctttcccggg gactttccgg ggactttccg ggactttcca tctgccatct 60
caattagtca gcaaccatag tcccgccccc aactccgccc atcccgcccc taactccgcc 120
cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga 180
ggccgcctcg gcctctgagc tattccagaa gtagtgagga ggcttttttg gaggcctagg 240
cttttgcaaa aagctt 256

<210> 407
<211> 24
<212> PRT
<213> Homo sapiens

<400> 407
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg
20

<210> 408
<211> 18
<212> PRT
<213> Homo sapiens

<400> 408
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser

<210> 409
<211> 21
<212> PRT
<213> Homo sapiens

<400> 409
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Ser Leu Asp Lys Arg
20

<210> 410
<211> 24
<212> PRT

<213> Homo sapiens

<400> 410
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg
20

<210> 411
<211> 18
<212> PRT
<213> Homo sapiens

<400> 411
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser

<210> 412
<211> 543
<212> DNA
<213> Homo sapiens

<400> 412
atgaaaagca tttactttgt ggctgggtta tttgtaatgc tggtacaagg cagctggcaa 60
cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 413
<211> 543
<212> DNA
<213> Homo sapiens

<400> 413
atgaaaagca tttactttgt ggctgggtta tttgtaatgc tggtacaagg cagctggcaa 60
cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 414
<211> 543
<212> DNA
<213> Homo sapiens

<400> 414
atgaaaagca tttactttgt ggctgggtta tttgtaatgc tggtacaagg cagctggcaa 60
cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300

gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 415
<211> 543
<212> DNA
<213> Homo sapiens

<400> 415
atgaaaagca tttactttgt ggctgggtta tttgtaatgc tggtacaagg cagctggcaa 60
cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 416
<211> 543
<212> DNA
<213> Homo sapiens

<400> 416
atgaaaagca tttactttgt ggctgggtta tttgtaatgc tggtacaagg cagctggcaa 60
cgttcccttc aagacacaga ggagaaatcc agatcattct cagcttccca ggcagaccca 120
ctcagtgatc ctgatcagat gaacgaggac aagcgccatt cacagggcac attcaccagt 180
gactacagca agtatctgga ctccaggcgt gcccaagatt ttgtgcagtg gttgatgaat 240
accaagagga acaggaataa cattgccaaa cgtcacgatg aatttgagag acatgctgaa 300
gggaccttta ccagtgatgt aagttcttat ttggaaggcc aagctgccaa ggaattcatt 360
gcttggctgg tgaaaggccg aggaaggcga gatttcccag aagaggtcgc cattgttgaa 420
gaacttggcc gcagacatgc tgatggttct ttctctgatg agatgaacac cattcttgat 480
aatcttgccg ccagggactt tataaactgg ttgattcaga ccaaaatcac tgacaggaaa 540
taa 543

<210> 417
<211> 180
<212> DNA
<213> Homo sapiens

<400> 417
cacgctgaag gtactttcac ttctgatgtt tcttcttact tggaaggtca agctgctaag 60
gaattcattg cttggttggt taagggtaga catgcagagg gaacatttac atcagacgtc 120
tcatcatatt tagagggaca ggcagcaaaa gagtttatag catggttagt aaaaggaagg 180

<210> 418
<211> 180
<212> DNA
<213> Homo sapiens

<400> 418
cacggtgaag gtactttcac ttctgatgtt tcttcttact tggaaggtca agctgctaag 60
gaattcattg cttggttggt taagggtaga catgcagagg gaacatttac atcagacgtc 120
tcatcatatt tagagggaca ggcagcaaaa gagtttatag catggttagt aaaaggaagg 180

<210> 419
<211> 669
<212> PRT
<213> Homo sapiens

<400> 419

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Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
 1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser
            20                  25                  30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
        35                  40                  45

Trp Leu Val Lys Gly Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val
    50                  55                  60

Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
65                  70                  75                  80

Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
                85                  90                  95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
            100                 105                 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365
```

```
Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
    370                 375                 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385                 390                 395                 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
                405                 410                 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
            420                 425                 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
        435                 440                 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
    450                 455                 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465                 470                 475                 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
                485                 490                 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
            500                 505                 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
        515                 520                 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
    530                 535                 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545                 550                 555                 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
                565                 570                 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
            580                 585                 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
        595                 600                 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
    610                 615                 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625                 630                 635                 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
                645                 650                 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 420
<211> 669
<212> PRT
<213> Homo sapiens

<400> 420

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15
```

```
Tyr Ser Arg Ser Leu Asp Lys Arg His Ala Glu Gly Thr Phe Thr Ser
            20                  25                  30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
        35                  40                  45

Trp Leu Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val
    50                  55                  60

Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
65                  70                  75                  80

Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
                85                  90                  95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
            100                 105                 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
```

370 375 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385 390 395 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
405 410 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
420 425 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
435 440 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
450 455 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465 470 475 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
485 490 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
500 505 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
515 520 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
530 535 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545 550 555 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
565 570 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
580 585 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
595 600 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
610 615 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625 630 635 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
645 650 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 421
<211> 669
<212> PRT
<213> Homo sapiens

<400> 421
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg His Ala Glu Gly Thr Phe Thr Ser

```
            20                  25                  30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
         35                  40                  45

Trp Leu Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val
     50                  55                  60

Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
 65                  70                  75                  80

Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
                 85                  90                  95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
            100                 105                 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
    370                 375                 380
```

```
Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385                 390                 395                 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
                405                 410                 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
            420                 425                 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
        435                 440                 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
    450                 455                 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465                 470                 475                 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
                485                 490                 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
            500                 505                 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
        515                 520                 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
    530                 535                 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545                 550                 555                 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
                565                 570                 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
            580                 585                 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
        595                 600                 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
    610                 615                 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625                 630                 635                 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
                645                 650                 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 422
<211> 667
<212> PRT
<213> Homo sapiens

<400> 422

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Gly Thr Phe Thr Ser Asp Val
            20                  25                  30
```

```
Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
          35                  40                  45

Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser
      50                  55                  60

Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys
 65                  70                  75                  80

Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
                 85                  90                  95

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
            100                 105                 110

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
        115                 120                 125

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
    130                 135                 140

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
145                 150                 155                 160

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
                165                 170                 175

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
            180                 185                 190

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
        195                 200                 205

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
    210                 215                 220

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
225                 230                 235                 240

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
                245                 250                 255

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
            260                 265                 270

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
        275                 280                 285

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
    290                 295                 300

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
305                 310                 315                 320

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
                325                 330                 335

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
            340                 345                 350

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
        355                 360                 365

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
    370                 375                 380

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
385                 390                 395                 400
```

```
Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
                405                 410                 415

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
            420                 425                 430

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
        435                 440                 445

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
    450                 455                 460

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
465                 470                 475                 480

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
                485                 490                 495

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
            500                 505                 510

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
        515                 520                 525

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
    530                 535                 540

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
545                 550                 555                 560

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
                565                 570                 575

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
            580                 585                 590

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
        595                 600                 605

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
    610                 615                 620

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
625                 630                 635                 640

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
                645                 650                 655

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 423
<211> 669
<212> PRT
<213> Homo sapiens

<400> 423

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg His Ser Glu Gly Thr Phe Thr Ser
            20                  25                  30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
        35                  40                  45
```

```
Trp Leu Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val
     50                  55                  60

Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
 65                  70                  75                  80

Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
                 85                  90                  95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
            100                 105                 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
    370                 375                 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385                 390                 395                 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
```

405 410 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
420 425 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
435 440 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
450 455 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465 470 475 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
485 490 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
500 505 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
515 520 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
530 535 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545 550 555 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
565 570 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
580 585 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
595 600 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
610 615 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625 630 635 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
645 650 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 424
<211> 669
<212> PRT
<213> Homo sapiens

<400> 424
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg His Ala Glu Gly Thr Phe Thr Ser
20 25 30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
35 40 45

Trp Leu Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val

```
     50                  55                  60

Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
 65                  70                  75                  80

Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
                85                  90                  95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
            100                 105                 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
    370                 375                 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385                 390                 395                 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
                405                 410                 415
```

```
Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
            420                 425                 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
        435                 440                 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
    450                 455                 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465                 470                 475                 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
                485                 490                 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
            500                 505                 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
        515                 520                 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
    530                 535                 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545                 550                 555                 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
                565                 570                 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
            580                 585                 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
        595                 600                 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
    610                 615                 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625                 630                 635                 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
                645                 650                 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 425
<211> 669
<212> PRT
<213> Homo sapiens

<400> 425

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser
            20                  25                  30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
        35                  40                  45

Trp Leu Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val
    50                  55                  60
```

```
Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu
 65                  70                  75                  80

Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
                 85                  90                  95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
            100                 105                 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
    370                 375                 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385                 390                 395                 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
                405                 410                 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
            420                 425                 430
```

```
Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
        435                 440                 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
    450                 455                 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465                 470                 475                 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
                485                 490                 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
            500                 505                 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
        515                 520                 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
    530                 535                 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545                 550                 555                 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
                565                 570                 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
            580                 585                 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
        595                 600                 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
    610                 615                 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625                 630                 635                 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
                645                 650                 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 426
<211> 180
<212> PRT
<213> Homo sapiens

<400> 426

```
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
  1               5                  10                  15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
             20                  25                  30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
         35                  40                  45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
     50                  55                  60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
 65                  70                  75                  80
```

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 427
<211> 180
<212> PRT
<213> Homo sapiens

<400> 427
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 428
<211> 180
<212> PRT
<213> Homo sapiens

<400> 428
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 429
<211> 180
<212> PRT
<213> Homo sapiens

<400> 429
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

```
Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
                 85                  90                  95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
            100                 105                 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
        115                 120                 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
    130                 135                 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145                 150                 155                 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
                165                 170                 175

Thr Asp Arg Lys
            180
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<210> 430
<211> 180
<212> PRT
<213> Homo sapiens

<400> 430

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Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
  1               5                  10                  15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
            20                  25                  30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
        35                  40                  45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
    50                  55                  60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65                  70                  75                  80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
                85                  90                  95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
            100                 105                 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
        115                 120                 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
    130                 135                 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145                 150                 155                 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
                165                 170                 175

Thr Asp Arg Lys
            180
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<210> 431

<211> 60
<212> PRT
<213> Homo sapiens

<400> 431
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His Ala
20 25 30

Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala
35 40 45

Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
50 55 60

<210> 432
<211> 60
<212> PRT
<213> Homo sapiens

<400> 432
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His Ala
20 25 30

Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala
35 40 45

Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
50 55 60

<210> 433
<211> 22
<212> DNA
<213> Homo sapiens

<400> 433
aggagcgtcg acaaaagaca cg 22

<210> 434
<211> 26
<212> DNA
<213> Homo sapiens

<400> 434
ctttaaatcg atgagcaacc tcactc 26

<210> 435
<211> 22
<212> DNA
<213> Homo sapiens

<400> 435
aggagcgtcg acaaaagaca cg 22

<210> 436
<211> 26
<212> DNA
<213> Homo sapiens

<400> 436
ctttaaatcg atgagcaacc tcactc 26

<210> 437
<211> 22
<212> DNA
<213> Homo sapiens

<400> 437
aggagcgtcg acaaaagaca cg 22

<210> 438
<211> 26
<212> DNA
<213> Homo sapiens

<400> 438
ctttaaatcg atgagcaacc tcactc 26

<210> 439
<211> 22
<212> DNA
<213> Homo sapiens

<400> 439
aggagcgtcg acaaaagaga ag 22

<210> 440
<211> 26
<212> DNA
<213> Homo sapiens

<400> 440
ctttaaatcg atgagcaacc tcactc 26

<210> 441
<211> 22
<212> DNA
<213> Homo sapiens

<400> 441
aggagcgtcg acaaaagaca ca 22

<210> 442
<211> 26
<212> DNA
<213> Homo sapiens

<400> 442
ctttaaatcg atgagcaacc tcactc 26

<210> 443
<211> 29
<212> DNA
<213> Homo sapiens

<400> 443
agcgtcgaca aaagacacgc tgaaggtac 29

<210> 444
<211> 21
<212> DNA
<213> Homo sapiens

<400> 444
catgatcttc aaatggacac t 21

<210> 445
<211> 22
<212> DNA

<213> Homo sapiens

<400> 445
aggagcgtcg acaaaagaca cg 22

<210> 446
<211> 21
<212> DNA
<213> Homo sapiens

<400> 446
catgatcttc aaatggacac t 21

<210> 447
<211> 674
<212> PRT
<213> Homo sapiens

<400> 447

```
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
  1               5                  10                  15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg His Gly Glu
             20                  25                  30

Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala
         35                  40                  45

Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His Gly Glu Gly Thr
     50                  55                  60

Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu
 65                  70                  75                  80

Phe Ile Ala Trp Leu Val Lys Gly Arg Asp Ala His Lys Ser Glu Val
                 85                  90                  95

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
            100                 105                 110

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
        115                 120                 125

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
    130                 135                 140

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
145                 150                 155                 160

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
                165                 170                 175

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
            180                 185                 190

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
        195                 200                 205

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
    210                 215                 220

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
225                 230                 235                 240

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
                245                 250                 255
```

```
Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
            260                 265                 270

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
        275                 280                 285

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
    290                 295                 300

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
305                 310                 315                 320

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
                325                 330                 335

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
            340                 345                 350

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
        355                 360                 365

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
    370                 375                 380

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
385                 390                 395                 400

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
                405                 410                 415

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
            420                 425                 430

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
        435                 440                 445

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
    450                 455                 460

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
465                 470                 475                 480

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
                485                 490                 495

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
            500                 505                 510

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
        515                 520                 525

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
    530                 535                 540

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
545                 550                 555                 560

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
                565                 570                 575

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
            580                 585                 590

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
        595                 600                 605

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
    610                 615                 620
```

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
625 630 635 640

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
645 650 655

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
660 665 670

Gly Leu

<210> 448
<211> 267
<212> DNA
<213> Homo sapiens

<400> 448
atgaacattt tctacatttt cttgttcttg ttgtctttcg ttcaaggttt ggaacacact 60
cacagaagag gttctttgga taagagacac ggtgaaggta ctttcacttc tgatgtttct 120
tcttacttgg aaggtcaagc tgctaaggaa ttcattgctt ggttggttaa gggtagacat 180
ggagagggaa catttacatc agacgtctca tcatatttag agggacaggc agcaaaagag 240
tttatagcat ggttagtaaa aggaagg 267

<210> 449
<211> 89
<212> PRT
<213> Homo sapiens

<400> 449
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg His Gly Glu
20 25 30

Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala
35 40 45

Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His Gly Glu Gly Thr
50 55 60

Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu
65 70 75 80

Phe Ile Ala Trp Leu Val Lys Gly Arg
85

<210> 450
<211> 20
<212> DNA
<213> Homo sapiens

<400> 450
gtcaatacct tcttgaacca 20

<210> 451
<211> 27
<212> DNA
<213> Homo sapiens

<400> 451
ctcccaaatc tttaaatcga tgagcaa 27

<210> 452
<211> 774
<212> PRT
<213> Homo sapiens

<400> 452
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser

325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

```
Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
    690                 695                 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705                 710                 715                 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
        755                 760                 765

Ser Leu Arg Ser Lys Glu
    770
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<210> 453
<211> 495
<212> DNA
<213> Homo sapiens

<400> 453
tgtgatctgc ctcaaaccca cagcctgggt tctagaagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 454
<211> 165
<212> PRT
<213> Homo sapiens

<400> 454
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Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
  1               5                  10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
             20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
         35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
     50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                 85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
```

```
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165
```

<210> 455
<211> 774
<212> PRT
<213> Homo sapiens

<400> 455

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285
```

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
705 710 715 720

Asn Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 456
<211> 495
<212> DNA
<213> Homo sapiens

<400> 456
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acttggaagc ctgtgtgatg 300
caggaggaga gggtgggaga aactcccctg atgaatgcgg actccatctt ggctgtgaag 360
aaatacttcc gaagaatcac tctctatctg acagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatcc ctctctttat caacaaactt gcaagaaaga 480
ttaaggagga aggaa 495

<210> 457
<211> 165
<212> PRT
<213> Homo sapiens

<400> 457
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn

```
            100                 105                 110

Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145                 150                 155                 160

Leu Arg Arg Lys Glu
                165
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<210> 458
<211> 38
<212> DNA
<213> Homo sapiens

<400> 458
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 459
<211> 39
<212> DNA
<213> Homo sapiens

<400> 459
gcgcatggcg cgccttattc cttcctcctt aatctttct 39

<210> 460
<211> 774
<212> PRT
<213> Homo sapiens

<400> 460

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160
```

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

```
Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
    610                 615                 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625                 630                 635                 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
                645                 650                 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
            660                 665                 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
        675                 680                 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
    690                 695                 700

Glu Ser Cys Val Met Gln Glu Val Gly Val Ile Glu Ser Pro Leu Met
705                 710                 715                 720

Tyr Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Ser Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ile Asn Leu Gln Lys
        755                 760                 765

Arg Leu Lys Ser Lys Glu
    770
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<210> 461
<211> 495
<212> DNA
<213> Homo sapiens

<400> 461
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggagtc ctgtgtgatg 300
caggaagtgg gggtgataga gtctcccctg atgtacgagg actccatcct ggctgtgagg 360
aaatacttcc aaagaatcac tctatatctg acagagaaga aatacagctc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatcc ttctctttat caatcaactt gcaaaaaaga 480
ttgaagagta aggaa 495

<210> 462
<211> 165
<212> PRT
<213> Homo sapiens

<400> 462
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ser Cys Val Met Gln Glu Val Gly Val Ile Glu Ser Pro Leu Met Tyr
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Ser Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ile Asn Leu Gln Lys Arg
145 150 155 160

Leu Lys Ser Lys Glu
165

<210> 463
<211> 38
<212> DNA
<213> Homo sapiens

<400> 463
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 464
<211> 38
<212> DNA
<213> Homo sapiens

<400> 464
gcgcatggcg cgcctcattc cttactcttc aatctttt 38

<210> 465
<211> 774
<212> PRT
<213> Homo sapiens

<400> 465
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

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His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
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385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Met
690 695 700

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
705 710 715 720

Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Lys Ile Phe Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 466
<211> 495
<212> DNA
<213> Homo sapiens

<400> 466
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acatggaagc ctgcgtgata 300
caggaggttg gggtggaaga gactcccctg atgaatgtgg actccatctt ggctgtgaag 360
aaatacttcc aaagaatcac tctttatctg acagagaaga aatacagccc ttgtgcttgg 420
gaggttgtca gagcagaaat catgagatcc ttctctttat caaaaatttt tcaagaaaga 480
ttaaggagga aggaa 495

<210> 467
<211> 165
<212> PRT
<213> Homo sapiens

<400> 467
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Met Glu
85 90 95

Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met Asn
100 105 110

Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Lys Ile Phe Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 468
<211> 38
<212> DNA
<213> Homo sapiens

<400> 468

caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 469
<211> 39
<212> DNA
<213> Homo sapiens

<400> 469
gcgcatggcg cgccttattc cttcctcctt aatctttct 39

<210> 470
<211> 774
<212> PRT
<213> Homo sapiens

<400> 470
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys

625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp
675 680 685

Leu Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
705 710 715 720

Asn Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 471
<211> 495
<212> DNA
<213> Homo sapiens

<400> 471
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaacctctt taccacaaaa gattcatctg ctgcttggga tgaggacctc 240
ctagacaaat tctgcaccga actctaccag cagctgaatg acttggaagc ctgtgtgatg 300
caggaggaga gggtgggaga aactcccctg atgaatgcgg actccatctt ggctgtgaag 360
aaatacttcc gaagaatcac tctctatctg acagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatcc ctctctttat caacaaactt gcaagaaaga 480
ttaaggagga aggaa 495

<210> 472
<211> 165
<212> PRT
<213> Homo sapiens

<400> 472
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp Leu
65 70 75 80

Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu

85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 473
<211> 38
<212> DNA
<213> Homo sapiens

<400> 473
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 474
<211> 39
<212> DNA
<213> Homo sapiens

<400> 474
gcgcatggcg cgccttattc cttcctcctt aatctttct 39

<210> 475
<211> 774
<212> PRT
<213> Homo sapiens

<400> 475
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala

515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
705 710 715 720

Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
725 730 735

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Arg Leu Arg Arg Lys Glu
770

<210> 476
<211> 495
<212> DNA
<213> Homo sapiens

<400> 476
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
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Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
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<212> DNA
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<212> DNA
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<213> Homo sapiens

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gtgctcctgc atctggaggt gggcgaccaa gtctggctcc aggtgtatgg ggaaggagag 660
cgtaatggac tctatgctga taatgacaat gactccacct tcacaggctt tcttctctac 720
catgacacca actga 735

<210> 531
<211> 735
<212> DNA
<213> Homo sapiens

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gcgggcatcc cagggcatcc gggccataat ggggccccag gccgtgatgg cagagatggc 180
acccctggtg agaagggtga gaaaggagat ccaggtctta ttggtcctaa gggagacatc 240
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acttacgtta ctatccccaa catgcccatt cgctttacca agatcttcta caatcagcaa 420
aaccactatg atggctccac tggtaaattc cactgcaaca ttcctgggct gtactacttt 480
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gctatgctct tcacctatga tcagtaccag gaaaataatg tggaccaggc ctccggctct 600
gtgctcctgc atctggaggt gggcgaccaa gtctggctcc aggtgtatgg ggaaggagag 660
cgtaatggac tctatgctga taatgacaat gactccacct tcacaggctt tcttctctac 720
catgacacca actga 735

<210> 532
<211> 249

<212> DNA
<213> Homo sapiens

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gctgctaagg aattcattgc ttggttggtt aagggtagac atggagaggg aacatttaca 180
tcagacgtct catcatattt agagggacag gcagcaaaag agtttatagc atggttagta 240
aaaggaagg 249

<210> 533
<211> 435
<212> DNA
<213> Homo sapiens

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ttagtaaaag gaagg 435

<210> 534
<211> 231
<212> DNA
<213> Homo sapiens

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gcttggttgg ttaagggtag acatggagag ggaacattta catcagacgt ctcatcatat 180
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<211> 435
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<213> Homo sapiens

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tctctcgaca aaagacacgg tgaaggtact ttcacttctg atgtttcttc ttacttggaa 300
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ttagtaaaag gaagg 435

<210> 536
<211> 249
<212> DNA
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gctgctaagg aattcattgc ttggttggtt aagggtagac atgcagaggg aacatttaca 180
tcagacgtct catcatattt agagggacag gcagcaaaag agtttatagc atggttagta 240
aaaggaagg 249

<210> 537
<211> 231
<212> DNA
<213> Homo sapiens

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<210> 538
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<212> DNA
<213> Homo sapiens

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ttgcaaccat tggctttgga aggttctttg caa 93

<210> 539
<211> 396
<212> DNA
<213> Homo sapiens

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ggcaggggcc ccatccttcc aggcaccaag gcctggatgg agaccgagga caccctgggc 240
cgtgtcctga gccccgagcc cgaccatgac agcctgtacc accctccgcc tgaggaggac 300
cagggcgagg agaggccccg gttgtgggtg atgccaaatc accaggtgct cctgggaccg 360
gaggaagacc aagaccacat ctaccacccc cagtag 396

<210> 540
<211> 108
<212> DNA
<213> Homo sapiens

<400> 540
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tacgcctccc tgcgccacta cctcaacctg gtcacccggc agcggtat 108

<210> 541
<211> 102
<212> DNA
<213> Homo sapiens

<400> 541
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tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 542
<211> 102
<212> DNA
<213> Homo sapiens

<400> 542
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tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 543
<211> 102
<212> DNA
<213> Homo sapiens

<400> 543
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<210> 544

<211> 192
<212> DNA
<213> Homo sapiens

<400> 544
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gaaagaggtt tcttctacac tccaaagact ggttacggtt cttcttctag aagagctcca 120
caaactggta ttgttgaaca atgttgtact tctatttgtt ctttgtacca attggaaaac 180
tactgtaact aa 192

<210> 545
<211> 192
<212> DNA
<213> Homo sapiens

<400> 545
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gaaagaggtt tcttctacac tccaaagact ggttacggtt cttcttctag aagagctcca 120
caaactggta ttgttgaaca atgttgtact tctatttgtt ctttgtacca attggaaaac 180
tactgtaact aa 192

<210> 546
<211> 90
<212> DNA
<213> Homo sapiens

<400> 546
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gaattcattg cttggttggt taagggtaga 90

<210> 547
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<212> DNA
<213> Homo sapiens

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gcgttgtgca gtcgggctct aagcaatgag attctgggcc tgaagttgcc tggcgagccg 120
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<210> 548
<211> 221
<212> DNA
<213> Homo sapiens

<400> 548
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ggacctggtg ctggttcctt gcaacctttg gctttggaag gttccttgca agaggcagag 120
gacctacagg taggacaggt agagctagga ggcggtccag gagcaggaag tctacagcca 180

ctagcactag agggaagtct acagtaaggc gcgccaggtc c 221

<210> 549
<211> 174
<212> DNA
<213> Homo sapiens

<400> 549
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gagcgcggct tcttctacac ccccaagacc gaggccgagg acctgcaggt gggcatcgtg 120
gagcagtgct gcacctccat ctgctccctg taccagctgg agaactactg caac 174

<210> 550
<211> 174
<212> DNA
<213> Homo sapiens

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gaaagaggtt tcttctacac tccaaagact gaagctgaag atttgcaagt tggtattgtt 120
gaacaatgtt gtacttctat ttgttctttg taccaattgg aaaactactg taac 174

<210> 551
<211> 351
<212> DNA
<213> Homo sapiens

<400> 551
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tactctgccg tggatgatgc ctcccacgag aaggagctga tcgaagcgct gcaagaagtc 180
ttgaagaagc tcaagagtaa acgtgttccc atctatgaga agaagtatgg ccaagtcccc 240
atgtgtgacg ccggtgagca gtgtgcagtg aggaaagggg caaggatcgg gaagctgtgt 300
gactgtcccc gaggaacctc ctgcaattcc ttcctcctga agtgcttatg a 351

<210> 552
<211> 396
<212> DNA
<213> Homo sapiens

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cgtgtcctga gccccgagcc cgaccatgac agcctgtacc accctccgcc tgaggaggac 300
cagggcgagg agaggccccg gttgtgggtg atgccaaatc accaggtgct cctgggaccg 360
gaggaagacc aagaccacat ctaccacccc cagtaa 396

<210> 553
<211> 102
<212> DNA
<213> Homo sapiens

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tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 554
<211> 102
<212> DNA
<213> Homo sapiens

<400> 554
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tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 555
<211> 771
<212> PRT
<213> Homo sapiens

<400> 555
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Thr Thr Ala Leu Ser Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser
20 25 30

Ser Asn Phe Gln Ser Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu
35 40 45

Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile
50 55 60

Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr
65 70 75 80

Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser
85 90 95

Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr
100 105 110

His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys
115 120 125

Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg
130 135 140

Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His
145 150 155 160

Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe
165 170 175

Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Ala His Lys Ser Glu
180 185 190

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
195 200 205

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
210 215 220

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
225 230 235 240

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
245 250 255

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
260 265 270

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
275 280 285

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
290 295 300

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
305 310 315 320

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
325 330 335

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
340 345 350

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
355 360 365

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
370 375 380

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
385 390 395 400

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
405 410 415

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
420 425 430

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
435 440 445

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
450 455 460

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
465 470 475 480

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
485 490 495

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
500 505 510

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
515 520 525

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
530 535 540

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
545 550 555 560

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
565 570 575

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
580 585 590

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
595 600 605

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
610 615 620

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
625 630 635 640

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
645 650 655

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
660 665 670

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe

675 680 685

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
690 695 700

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
705 710 715 720

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
725 730 735

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
740 745 750

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
755 760 765

Leu Gly Leu
770

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<211> 1010
<212> PRT
<213> Homo sapiens

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Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
20 25 30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
35 40 45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
50 55 60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65 70 75 80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
85 90 95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
100 105 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
115 120 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
130 135 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145 150 155 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
165 170 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
180 185 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
195 200 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
210 215 220

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Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225                 230                 235                 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                245                 250                 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            260                 265                 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        275                 280                 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    290                 295                 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305                 310                 315                 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                325                 330                 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            340                 345                 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        355                 360                 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    370                 375                 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385                 390                 395                 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                405                 410                 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            420                 425                 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        435                 440                 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    450                 455                 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465                 470                 475                 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                485                 490                 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            500                 505                 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        515                 520                 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
    530                 535                 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545                 550                 555                 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
                565                 570                 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
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Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Lys Pro Leu Gln Ser
        595                 600                 605

Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val
    610                 615                 620

Pro Gly Gly Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu
625                 630                 635                 640

Glu Asn Val Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val
                645                 650                 655

Pro Ser Gln Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp
            660                 665                 670

Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn
        675                 680                 685

Ile Val Arg Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr
    690                 695                 700

Glu Asp Phe Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile
705                 710                 715                 720

Pro Arg His Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser
                725                 730                 735

Cys Gln Asn His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val
            740                 745                 750

Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu
        755                 760                 765

Thr Lys Thr Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu
    770                 775                 780

Thr Leu Glu Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser
785                 790                 795                 800

Thr Lys Ser Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys
                805                 810                 815

Gly Cys Asp Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu
            820                 825                 830

Pro Phe Phe Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu
        835                 840                 845

Thr Arg Leu Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val
    850                 855                 860

Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser
865                 870                 875                 880

His Glu Glu Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala
                885                 890                 895

Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser
            900                 905                 910

Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala
        915                 920                 925

Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro
    930                 935                 940
```

```
Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu
945                 950                 955                 960

Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro
                965                 970                 975

Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val
            980                 985                 990

Pro Thr Leu Lys Tyr His Tyr Glu  Gly Met Ser Val Ala  Glu Cys Gly
        995                 1000                1005

Cys Arg
    1010
```

<210> 557
<211> 1010
<212> PRT
<213> Homo sapiens

```
<400> 557
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
  1               5                  10                  15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
             20                  25                  30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
         35                  40                  45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
     50                  55                  60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
 65                  70                  75                  80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                 85                  90                  95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            100                 105                 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        115                 120                 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    130                 135                 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145                 150                 155                 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                165                 170                 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            180                 185                 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        195                 200                 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    210                 215                 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225                 230                 235                 240
```

```
Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                245                 250                 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            260                 265                 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        275                 280                 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    290                 295                 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305                 310                 315                 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                325                 330                 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            340                 345                 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        355                 360                 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    370                 375                 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385                 390                 395                 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                405                 410                 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            420                 425                 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        435                 440                 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    450                 455                 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465                 470                 475                 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                485                 490                 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            500                 505                 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        515                 520                 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
    530                 535                 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545                 550                 555                 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
                565                 570                 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
            580                 585                 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Lys Pro Leu Gln Ser
        595                 600                 605
```

```
Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val
    610                 615                 620

Pro Gly Gly Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu
625                 630                 635                 640

Glu Asn Val Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val
                645                 650                 655

Pro Ser Gln Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp
            660                 665                 670

Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn
        675                 680                 685

Ile Val Arg Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr
    690                 695                 700

Glu Asp Phe Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile
705                 710                 715                 720

Pro Arg His Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser
                725                 730                 735

Cys Gln Asn His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val
            740                 745                 750

Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu
        755                 760                 765

Thr Lys Thr Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu
    770                 775                 780

Thr Leu Glu Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser
785                 790                 795                 800

Thr Lys Ser Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys
                805                 810                 815

Gly Cys Asp Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu
            820                 825                 830

Pro Phe Phe Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu
        835                 840                 845

Thr Arg Leu Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val
    850                 855                 860

Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser
865                 870                 875                 880

His Glu Glu Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala
                885                 890                 895

Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser
            900                 905                 910

Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala
        915                 920                 925

Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro
    930                 935                 940

Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu
945                 950                 955                 960

Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro
```

965 970 975

Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val
980 985 990

Pro Thr Leu Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly
995 1000 1005

Cys Arg
1010

<210> 558
<211> 1010
<212> PRT
<213> Homo sapiens

<400> 558
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
20 25 30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
35 40 45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
50 55 60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65 70 75 80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
85 90 95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
100 105 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
115 120 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
130 135 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145 150 155 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
165 170 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
180 185 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
195 200 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
210 215 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225 230 235 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
245 250 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala

```
          260                 265                 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        275                 280                 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    290                 295                 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305                 310                 315                 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                325                 330                 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            340                 345                 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        355                 360                 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    370                 375                 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385                 390                 395                 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                405                 410                 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            420                 425                 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        435                 440                 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    450                 455                 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465                 470                 475                 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                485                 490                 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            500                 505                 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        515                 520                 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
    530                 535                 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545                 550                 555                 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
                565                 570                 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
            580                 585                 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Lys Pro Leu Gln Ser
        595                 600                 605

Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val
    610                 615                 620
```

```
Pro Gly Gly Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu
625                 630                 635                 640

Glu Asn Val Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val
                645                 650                 655

Pro Ser Gln Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp
            660                 665                 670

Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn
        675                 680                 685

Ile Val Arg Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr
    690                 695                 700

Glu Asp Phe Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile
705                 710                 715                 720

Pro Arg His Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser
                725                 730                 735

Cys Gln Asn His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val
            740                 745                 750

Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu
        755                 760                 765

Thr Lys Thr Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu
    770                 775                 780

Thr Leu Glu Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser
785                 790                 795                 800

Thr Lys Ser Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys
                805                 810                 815

Gly Cys Asp Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu
            820                 825                 830

Pro Phe Phe Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu
        835                 840                 845

Thr Arg Leu Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val
    850                 855                 860

Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser
865                 870                 875                 880

His Glu Glu Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala
                885                 890                 895

Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser
            900                 905                 910

Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala
        915                 920                 925

Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro
    930                 935                 940

Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu
945                 950                 955                 960

Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro
                965                 970                 975

Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val
            980                 985                 990
```

```
Pro Thr Leu Lys Tyr His Tyr Glu  Gly Met Ser Val Ala  Glu Cys Gly
        995                 1000                1005

Cys Arg
    1010
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<210> 559
<211> 1010
<212> PRT
<213> Homo sapiens

<400> 559

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Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
  1               5                  10                  15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
            20                  25                  30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
        35                  40                  45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
    50                  55                  60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65                  70                  75                  80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                85                  90                  95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            100                 105                 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        115                 120                 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    130                 135                 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145                 150                 155                 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                165                 170                 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            180                 185                 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        195                 200                 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    210                 215                 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225                 230                 235                 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                245                 250                 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            260                 265                 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
```

275 280 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
290 295 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305 310 315 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
325 330 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
340 345 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
355 360 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
370 375 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385 390 395 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
405 410 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
420 425 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
435 440 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
450 455 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465 470 475 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
485 490 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
500 505 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
515 520 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
530 535 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545 550 555 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
565 570 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
580 585 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Lys Pro Leu Gln Ser
595 600 605

Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val
610 615 620

Pro Gly Gly Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu
625 630 635 640

Glu Asn Val Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val
645 650 655

Pro Ser Gln Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp
660 665 670

Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn
675 680 685

Ile Val Arg Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr
690 695 700

Glu Asp Phe Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile
705 710 715 720

Pro Arg His Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser
725 730 735

Cys Gln Asn His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val
740 745 750

Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu
755 760 765

Thr Lys Thr Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu
770 775 780

Thr Leu Glu Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser
785 790 795 800

Thr Lys Ser Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys
805 810 815

Gly Cys Asp Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu
820 825 830

Pro Phe Phe Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu
835 840 845

Thr Arg Leu Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val
850 855 860

Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser
865 870 875 880

His Glu Glu Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala
885 890 895

Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser
900 905 910

Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala
915 920 925

Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro
930 935 940

Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu
945 950 955 960

Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro
965 970 975

Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val
980 985 990

Pro Thr Leu Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly
995 1000 1005

Cys Arg
1010

<210> 560
<211> 1010
<212> PRT
<213> Homo sapiens

<400> 560
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
1 5 10 15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
20 25 30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
35 40 45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
50 55 60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65 70 75 80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
85 90 95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
100 105 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
115 120 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
130 135 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145 150 155 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
165 170 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
180 185 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
195 200 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
210 215 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225 230 235 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
245 250 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
260 265 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
275 280 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
290 295 300

```
Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305                 310                 315                 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                325                 330                 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            340                 345                 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        355                 360                 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    370                 375                 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385                 390                 395                 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                405                 410                 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            420                 425                 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        435                 440                 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    450                 455                 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465                 470                 475                 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                485                 490                 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            500                 505                 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        515                 520                 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
    530                 535                 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545                 550                 555                 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
                565                 570                 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
            580                 585                 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Lys Pro Leu Gln Ser
        595                 600                 605

Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val
    610                 615                 620

Pro Gly Gly Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu
625                 630                 635                 640

Glu Asn Val Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val
                645                 650                 655

Pro Ser Gln Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp
            660                 665                 670
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Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn
675 680 685

Ile Val Arg Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr
690 695 700

Glu Asp Phe Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile
705 710 715 720

Pro Arg His Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser
725 730 735

Cys Gln Asn His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val
740 745 750

Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu
755 760 765

Thr Lys Thr Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu
770 775 780

Thr Leu Glu Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser
785 790 795 800

Thr Lys Ser Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys
805 810 815

Gly Cys Asp Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu
820 825 830

Pro Phe Phe Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu
835 840 845

Thr Arg Leu Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val
850 855 860

Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser
865 870 875 880

His Glu Glu Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala
885 890 895

Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser
900 905 910

Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala
915 920 925

Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro
930 935 940

Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu
945 950 955 960

Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro
965 970 975

Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val
980 985 990

Pro Thr Leu Lys Tyr His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly
995 1000 1005

Cys Arg
1010

<210> 561
<211> 1010
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<213> Homo sapiens

<400> 561
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
1 5 10 15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
20 25 30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
35 40 45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
50 55 60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65 70 75 80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
85 90 95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
100 105 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
115 120 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
130 135 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145 150 155 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
165 170 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
180 185 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
195 200 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
210 215 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225 230 235 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
245 250 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
260 265 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
275 280 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
290 295 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305 310 315 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn

325 330 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
340 345 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
355 360 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
370 375 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385 390 395 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
405 410 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
420 425 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
435 440 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
450 455 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465 470 475 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
485 490 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
500 505 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
515 520 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
530 535 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545 550 555 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
565 570 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
580 585 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Lys Pro Leu Gln Ser
595 600 605

Trp Gly Arg Gly Ser Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val
610 615 620

Pro Gly Gly Gly Leu Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu
625 630 635 640

Glu Asn Val Lys Val Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val
645 650 655

Pro Ser Gln Asp Lys Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp
660 665 670

Leu Tyr Asn Arg Tyr Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn
675 680 685

```
Ile Val Arg Ser Phe Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr
    690                 695                 700

Glu Asp Phe Pro Phe Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile
705                 710                 715                 720

Pro Arg His Glu Gln Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser
                725                 730                 735

Cys Gln Asn His Val Asp Pro Ser His Asp Leu Lys Gly Ser Val Val
            740                 745                 750

Ile Tyr Asp Val Leu Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu
        755                 760                 765

Thr Lys Thr Phe Leu Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu
    770                 775                 780

Thr Leu Glu Val Ser Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser
785                 790                 795                 800

Thr Lys Ser Lys Asn Lys Leu Glu Val Thr Val Glu Ser His Arg Lys
                805                 810                 815

Gly Cys Asp Thr Leu Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu
            820                 825                 830

Pro Phe Phe Val Val Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu
        835                 840                 845

Thr Arg Leu Glu Leu Arg Glu Met Ile Ser His Glu Gln Glu Ser Val
    850                 855                 860

Leu Lys Lys Leu Ser Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser
865                 870                 875                 880

His Glu Glu Asp Thr Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala
                885                 890                 895

Arg Arg Lys Arg Ser Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser
            900                 905                 910

Leu Arg Val Asn Phe Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala
        915                 920                 925

Pro Lys Glu Tyr Glu Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro
    930                 935                 940

Leu Ala Asp Asp Val Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu
945                 950                 955                 960

Val His Leu Lys Phe Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro
                965                 970                 975

Thr Lys Leu Ser Pro Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val
            980                 985                 990

Pro Thr Leu Lys Tyr His Tyr Glu  Gly Met Ser Val Ala  Glu Cys Gly
        995                 1000                1005

Cys Arg
    1010
```

<210> 562
<211> 671

<212> PRT
<213> Homo sapiens

<400> 562
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly
20 25 30

Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe
35 40 45

Phe Tyr Thr Pro Lys Thr Lys Arg Gly Gly Gly Pro Gly Arg Gly Lys
50 55 60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg
85 90 95

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
100 105 110

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
115 120 125

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
130 135 140

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
145 150 155 160

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
165 170 175

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
180 185 190

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
195 200 205

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
210 215 220

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
225 230 235 240

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
245 250 255

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
260 265 270

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
275 280 285

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
290 295 300

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
305 310 315 320

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
325 330 335

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu

```
            340                 345                 350

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
        355                 360                 365

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
    370                 375                 380

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
385                 390                 395                 400

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
                405                 410                 415

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
            420                 425                 430

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
        435                 440                 445

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
    450                 455                 460

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
465                 470                 475                 480

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
                485                 490                 495

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
            500                 505                 510

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
        515                 520                 525

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
    530                 535                 540

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
545                 550                 555                 560

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
                565                 570                 575

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
            580                 585                 590

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
        595                 600                 605

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
    610                 615                 620

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
625                 630                 635                 640

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
                645                 650                 655

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665                 670
```

<210> 563
<211> 671
<212> PRT
<213> Homo sapiens

<400> 563

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
 1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350
```

```
Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu
    610                 615                 620

Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Lys
625                 630                 635                 640

Arg Gly Gly Gly Pro Gly Arg Gly Lys Arg Gly Ile Val Glu Gln Cys
                645                 650                 655

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
            660                 665                 670
```

<210> 564
<211> 667
<212> PRT
<213> Homo sapiens

<400> 564

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
 1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly
            20                  25                  30

Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe
        35                  40                  45

Phe Tyr Thr Pro Lys Thr Gly Gly Gly Pro Gly Lys Lys Gly Ile Val
    50                  55                  60

Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr
65                  70                  75                  80

Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
                85                  90                  95

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
            100                 105                 110

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
        115                 120                 125

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
    130                 135                 140

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
145                 150                 155                 160

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
                165                 170                 175

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
            180                 185                 190

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
        195                 200                 205

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
    210                 215                 220

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
225                 230                 235                 240

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
                245                 250                 255

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
            260                 265                 270

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
        275                 280                 285

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
    290                 295                 300

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
305                 310                 315                 320

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
                325                 330                 335

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
            340                 345                 350

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
        355                 360                 365
```

```
Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
    370                 375                 380

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
385                 390                 395                 400

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
                405                 410                 415

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
            420                 425                 430

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
        435                 440                 445

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
    450                 455                 460

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
465                 470                 475                 480

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
                485                 490                 495

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
            500                 505                 510

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
        515                 520                 525

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
    530                 535                 540

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
545                 550                 555                 560

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
                565                 570                 575

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
            580                 585                 590

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
        595                 600                 605

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
    610                 615                 620

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
625                 630                 635                 640

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
                645                 650                 655

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 565
<211> 667
<212> PRT
<213> Homo sapiens

<400> 565

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15
```

```
Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
```

```
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu
    610                 615                 620

Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly
625                 630                 635                 640

Gly Gly Pro Gly Lys Lys Gly Ile Val Glu Gln Cys Cys Thr Ser Ile
                645                 650                 655

Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
            660                 665


<210> 566
<211> 667
<212> PRT
<213> Homo sapiens

<400> 566
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
  1               5                  10                  15

Ile Ser Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu
             20                  25                  30
```

```
Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
         35                  40                  45

Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val
     50                  55                  60

Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr
 65                  70                  75                  80

Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
                 85                  90                  95

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
            100                 105                 110

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
        115                 120                 125

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
    130                 135                 140

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
145                 150                 155                 160

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
                165                 170                 175

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
            180                 185                 190

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
        195                 200                 205

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
    210                 215                 220

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
225                 230                 235                 240

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
                245                 250                 255

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
            260                 265                 270

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
        275                 280                 285

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
    290                 295                 300

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
305                 310                 315                 320

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
                325                 330                 335

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
            340                 345                 350

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
        355                 360                 365

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
    370                 375                 380

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
```

385 390 395 400

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
405 410 415

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
420 425 430

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
435 440 445

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
450 455 460

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
465 470 475 480

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
485 490 495

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
500 505 510

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
515 520 525

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
530 535 540

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
545 550 555 560

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
565 570 575

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
580 585 590

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
595 600 605

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
610 615 620

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
625 630 635 640

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
645 650 655

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 567
<211> 666
<212> PRT
<213> Homo sapiens

<400> 567
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala
20 25 30

Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr

```
        35                  40                  45

Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu
     50                  55                  60

Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys
 65                  70                  75                  80

Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
                 85                  90                  95

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
            100                 105                 110

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
        115                 120                 125

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
    130                 135                 140

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
145                 150                 155                 160

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
                165                 170                 175

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
            180                 185                 190

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
        195                 200                 205

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
    210                 215                 220

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
225                 230                 235                 240

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
                245                 250                 255

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
            260                 265                 270

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
        275                 280                 285

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
    290                 295                 300

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
305                 310                 315                 320

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
                325                 330                 335

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
            340                 345                 350

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
        355                 360                 365

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
    370                 375                 380

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
385                 390                 395                 400
```

```
Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
                405                 410                 415

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
            420                 425                 430

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
        435                 440                 445

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
    450                 455                 460

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
465                 470                 475                 480

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
                485                 490                 495

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
            500                 505                 510

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
        515                 520                 525

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
    530                 535                 540

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
545                 550                 555                 560

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
                565                 570                 575

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
            580                 585                 590

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
        595                 600                 605

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
    610                 615                 620

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
625                 630                 635                 640

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
                645                 650                 655

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665


<210> 568
<211> 667
<212> PRT
<213> Homo sapiens

<400> 568
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
  1               5                  10                  15

Ile Ser Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu
             20                  25                  30

Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
         35                  40                  45

Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val
```

```
     50                  55                  60

Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr
 65                  70                  75                  80

Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
                 85                  90                  95

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
            100                 105                 110

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
        115                 120                 125

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
    130                 135                 140

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
145                 150                 155                 160

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
                165                 170                 175

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
            180                 185                 190

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
        195                 200                 205

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
    210                 215                 220

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
225                 230                 235                 240

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
                245                 250                 255

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
            260                 265                 270

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
        275                 280                 285

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
    290                 295                 300

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
305                 310                 315                 320

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
                325                 330                 335

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
            340                 345                 350

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
        355                 360                 365

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
    370                 375                 380

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
385                 390                 395                 400

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
                405                 410                 415
```

```
Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
            420                 425                 430

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
        435                 440                 445

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
    450                 455                 460

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
465                 470                 475                 480

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
                485                 490                 495

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
            500                 505                 510

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
        515                 520                 525

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
    530                 535                 540

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
545                 550                 555                 560

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
                565                 570                 575

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
            580                 585                 590

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
        595                 600                 605

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
    610                 615                 620

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
625                 630                 635                 640

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
                645                 650                 655

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 569
<211> 662
<212> PRT
<213> Homo sapiens

<400> 569

```
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
  1               5                  10                  15

Ile Ser Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu
            20                  25                  30

Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
        35                  40                  45

Thr Gly Gly Gly Pro Gly Lys Arg Gly Ile Val Glu Gln Cys Cys Thr
    50                  55                  60
```

```
Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Asp Ala His
 65                  70                  75                  80

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
                 85                  90                  95

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
            100                 105                 110

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
        115                 120                 125

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
    130                 135                 140

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
145                 150                 155                 160

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
                165                 170                 175

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
            180                 185                 190

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
        195                 200                 205

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
    210                 215                 220

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
225                 230                 235                 240

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
                245                 250                 255

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
            260                 265                 270

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
        275                 280                 285

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
    290                 295                 300

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
305                 310                 315                 320

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
                325                 330                 335

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
            340                 345                 350

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
        355                 360                 365

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
    370                 375                 380

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
385                 390                 395                 400

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
                405                 410                 415

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
            420                 425                 430
```

```
Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
        435                 440                 445

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
    450                 455                 460

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
465                 470                 475                 480

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
                485                 490                 495

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
            500                 505                 510

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
        515                 520                 525

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
    530                 535                 540

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
545                 550                 555                 560

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
                565                 570                 575

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
            580                 585                 590

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
        595                 600                 605

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
    610                 615                 620

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
625                 630                 635                 640

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
                645                 650                 655

Gln Ala Ala Leu Gly Leu
            660
```

<210> 570
<211> 769
<212> PRT
<213> Homo sapiens

<400> 570

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
  1               5                  10                  15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
             20                  25                  30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
         35                  40                  45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
     50                  55                  60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
 65                  70                  75                  80
```

```
Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                 85                  90                  95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            100                 105                 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        115                 120                 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    130                 135                 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145                 150                 155                 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                165                 170                 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            180                 185                 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        195                 200                 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    210                 215                 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225                 230                 235                 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                245                 250                 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            260                 265                 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        275                 280                 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    290                 295                 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305                 310                 315                 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                325                 330                 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            340                 345                 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        355                 360                 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    370                 375                 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385                 390                 395                 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                405                 410                 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            420                 425                 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        435                 440                 445
```

```
Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    450                 455                 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465                 470                 475                 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                485                 490                 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            500                 505                 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        515                 520                 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
    530                 535                 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545                 550                 555                 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
                565                 570                 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
            580                 585                 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Met Ser Tyr Asn Leu
        595                 600                 605

Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu
    610                 615                 620

Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn
625                 630                 635                 640

Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu
                645                 650                 655

Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile
            660                 665                 670

Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu
        675                 680                 685

Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val
    690                 695                 700

Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met
705                 710                 715                 720

Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu
                725                 730                 735

Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu
            740                 745                 750

Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg
        755                 760                 765

Asn
```

<210> 571
<211> 769

<212> PRT
<213> Homo sapiens

<400> 571
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Gly Val
1 5 10 15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
20 25 30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
35 40 45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
50 55 60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65 70 75 80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
85 90 95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
100 105 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
115 120 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
130 135 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145 150 155 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
165 170 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
180 185 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
195 200 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
210 215 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225 230 235 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
245 250 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
260 265 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
275 280 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
290 295 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305 310 315 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
325 330 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr

```
           340                 345                 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        355                 360                 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    370                 375                 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385                 390                 395                 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                405                 410                 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            420                 425                 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        435                 440                 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    450                 455                 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465                 470                 475                 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                485                 490                 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            500                 505                 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        515                 520                 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
    530                 535                 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545                 550                 555                 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
                565                 570                 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
            580                 585                 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Met Ser Tyr Asn Leu
        595                 600                 605

Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu
    610                 615                 620

Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn
625                 630                 635                 640

Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu
                645                 650                 655

Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile
            660                 665                 670

Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu
        675                 680                 685

Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val
    690                 695                 700
```

```
Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met
705                 710                 715                 720

Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu
                725                 730                 735

Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu
            740                 745                 750

Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg
        755                 760                 765

Asn
```

<210> 572
<211> 769
<212> PRT
<213> Homo sapiens

<400> 572

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Gly Gly Val
  1               5                  10                  15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
             20                  25                  30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
         35                  40                  45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
     50                  55                  60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
 65                  70                  75                  80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                 85                  90                  95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            100                 105                 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        115                 120                 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    130                 135                 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145                 150                 155                 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                165                 170                 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            180                 185                 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        195                 200                 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    210                 215                 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
225                 230                 235                 240
```

```
Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                245                 250                 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            260                 265                 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        275                 280                 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    290                 295                 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305                 310                 315                 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                325                 330                 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            340                 345                 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        355                 360                 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    370                 375                 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385                 390                 395                 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                405                 410                 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            420                 425                 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        435                 440                 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    450                 455                 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465                 470                 475                 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                485                 490                 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            500                 505                 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        515                 520                 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
    530                 535                 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545                 550                 555                 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
                565                 570                 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
            580                 585                 590

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Met Ser Tyr Asn Leu
        595                 600                 605
```

Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu
610 615 620

Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn
625 630 635 640

Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu
645 650 655

Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile
660 665 670

Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu Thr Ile Val Glu
675 680 685

Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His Leu Lys Thr Val
690 695 700

Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg Gly Lys Leu Met
705 710 715 720

Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu
725 730 735

Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile Val Arg Val Glu
740 745 750

Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg
755 760 765

Asn

<210> 573
<211> 623
<212> PRT
<213> Homo sapiens

<400> 573
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Gly Cys Lys Asn Phe Phe Trp
20 25 30

Lys Thr Phe Thr Ser Cys Asp Ala His Lys Ser Glu Val Ala His Arg
35 40 45

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
50 55 60

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
65 70 75 80

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
85 90 95

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
100 105 110

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
115 120 125

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
130 135 140

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val

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145                 150                 155                 160

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
                165                 170                 175

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
            180                 185                 190

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
        195                 200                 205

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
    210                 215                 220

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
225                 230                 235                 240

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
                245                 250                 255

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
            260                 265                 270

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
        275                 280                 285

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
    290                 295                 300

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
305                 310                 315                 320

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
                325                 330                 335

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
            340                 345                 350

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
        355                 360                 365

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
    370                 375                 380

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
385                 390                 395                 400

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
                405                 410                 415

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
            420                 425                 430

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
        435                 440                 445

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
    450                 455                 460

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
465                 470                 475                 480

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
                485                 490                 495

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
            500                 505                 510
```

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
515 520 525

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
530 535 540

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
545 550 555 560

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
565 570 575

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
580 585 590

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
595 600 605

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
610 615 620

<210> 574
<211> 654
<212> PRT
<213> Homo sapiens

<400> 574
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser
20 25 30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
35 40 45

Trp Leu Val Lys Gly Arg Gly Arg Arg Asp Phe Pro Glu Glu Val Ala
50 55 60

Ile Val Glu Glu Leu Asp Ala His Lys Ser Glu Val Ala His Arg Phe
65 70 75 80

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
85 90 95

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
100 105 110

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
115 120 125

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
130 135 140

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
145 150 155 160

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
165 170 175

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
180 185 190

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
195 200 205

```
Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
    210                 215                 220

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
225                 230                 235                 240

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
                245                 250                 255

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
            260                 265                 270

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
        275                 280                 285

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
    290                 295                 300

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
305                 310                 315                 320

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
                325                 330                 335

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
            340                 345                 350

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
        355                 360                 365

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
    370                 375                 380

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
385                 390                 395                 400

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
                405                 410                 415

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
            420                 425                 430

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
        435                 440                 445

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
    450                 455                 460

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
465                 470                 475                 480

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
                485                 490                 495

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
            500                 505                 510

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
        515                 520                 525

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
    530                 535                 540

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
545                 550                 555                 560

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
                565                 570                 575
```

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Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
            580                 585                 590

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
        595                 600                 605

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
    610                 615                 620

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
625                 630                 635                 640

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                645                 650
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<210> 575
<211> 666
<212> PRT
<213> Homo sapiens

<400> 575

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Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala
            20                  25                  30

Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
        35                  40                  45

Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu
    50                  55                  60

Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys
65                  70                  75                  80

Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
                85                  90                  95

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
            100                 105                 110

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
        115                 120                 125

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
    130                 135                 140

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
145                 150                 155                 160

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
                165                 170                 175

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
            180                 185                 190

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
        195                 200                 205

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
    210                 215                 220

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
225                 230                 235                 240
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Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
                245                 250                 255

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
            260                 265                 270

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
        275                 280                 285

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
    290                 295                 300

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
305                 310                 315                 320

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
                325                 330                 335

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
            340                 345                 350

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
        355                 360                 365

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
    370                 375                 380

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
385                 390                 395                 400

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
                405                 410                 415

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
            420                 425                 430

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
        435                 440                 445

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
    450                 455                 460

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
465                 470                 475                 480

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
                485                 490                 495

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
            500                 505                 510

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
        515                 520                 525

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
    530                 535                 540

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
545                 550                 555                 560

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
                565                 570                 575

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
            580                 585                 590

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
        595                 600                 605
```

```
Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
     610                 615                 620

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
625                 630                 635                 640

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
                645                 650                 655

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
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<210> 576
<211> 733
<212> PRT
<213> Homo sapiens

<400> 576

```
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
  1               5                  10                  15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
            20                  25                  30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
        35                  40                  45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
    50                  55                  60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65                  70                  75                  80

Ser Leu Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly Ser His Leu
                85                  90                  95

Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr
            100                 105                 110

Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly
        115                 120                 125

Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu
    130                 135                 140

Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
145                 150                 155                 160

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
                165                 170                 175

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
            180                 185                 190

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
        195                 200                 205

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
    210                 215                 220

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
225                 230                 235                 240

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
                245                 250                 255
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Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
260 265 270

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
275 280 285

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
290 295 300

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
305 310 315 320

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
325 330 335

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
340 345 350

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
355 360 365

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
370 375 380

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
385 390 395 400

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
405 410 415

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
420 425 430

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
435 440 445

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
450 455 460

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
465 470 475 480

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
485 490 495

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
500 505 510

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
515 520 525

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
530 535 540

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
545 550 555 560

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
565 570 575

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
580 585 590

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
595 600 605

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys

610 615 620

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
625 630 635 640

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
645 650 655

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
660 665 670

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
675 680 685

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
690 695 700

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
705 710 715 720

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
725 730

<210> 577
<211> 623
<212> PRT
<213> Homo sapiens

<400> 577
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu

195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Gly Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
610 615 620

<210> 578
<211> 637
<212> PRT
<213> Homo sapiens

<400> 578
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Ala Asn Ser Asn Pro Ala Met
20 25 30

Ala Pro Arg Glu Arg Lys Ala Gly Cys Lys Asn Phe Phe Trp Lys Thr
35 40 45

Phe Thr Ser Cys Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
50 55 60

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
65 70 75 80

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
85 90 95

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
100 105 110

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
115 120 125

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
130 135 140

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
145 150 155 160

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
165 170 175

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
180 185 190

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
195 200 205

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
210 215 220

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
225 230 235 240

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
245 250 255

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser

260 265 270

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
275 280 285

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
290 295 300

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
305 310 315 320

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
325 330 335

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
340 345 350

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
355 360 365

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
370 375 380

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
385 390 395 400

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
405 410 415

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
420 425 430

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
435 440 445

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
450 455 460

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
465 470 475 480

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
485 490 495

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
500 505 510

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
515 520 525

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
530 535 540

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
545 550 555 560

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
565 570 575

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
580 585 590

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
595 600 605

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
610 615 620

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 579
<211> 637
<212> PRT
<213> Homo sapiens

<400> 579
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ser Ala Asn Ser Asn Pro Ala Met Ala Pro Arg Glu Arg Lys Ala
610 615 620

Gly Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
625 630 635

<210> 580
<211> 690
<212> PRT
<213> Homo sapiens

<400> 580
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu
20 25 30

Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
35 40 45

Thr Arg Arg Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly
50 55 60

Gly Gly Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser
65 70 75 80

Leu Gln Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser
85 90 95

Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val
100 105 110

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
115 120 125

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
130 135 140

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
145 150 155 160

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
165 170 175

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
180 185 190

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
195 200 205

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
210 215 220

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
225 230 235 240

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
245 250 255

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
260 265 270

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
275 280 285

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
290 295 300

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
305 310 315 320

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
325 330 335

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
340 345 350

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
355 360 365

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
370 375 380

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
385 390 395 400

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
405 410 415

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
420 425 430

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
435 440 445

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
450 455 460

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
465 470 475 480

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
485 490 495

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
500 505 510

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
515 520 525

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
530 535 540

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
545 550 555 560

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
565 570 575

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
580 585 590

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
595 600 605

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
610 615 620

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
625 630 635 640

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
645 650 655

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
660 665 670

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
675 680 685

Gly Leu
690

<210> 581

<211> 677
<212> PRT
<213> Homo sapiens

<400> 581

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Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
  1               5                  10                  15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Phe Val Asn
             20                  25                  30

Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys
         35                  40                  45

Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr Gly Ser Ser
     50                  55                  60

Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser
 65                  70                  75                  80

Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Asp Ala His Lys
                 85                  90                  95

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
            100                 105                 110

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
        115                 120                 125

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
    130                 135                 140

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
145                 150                 155                 160

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
                165                 170                 175

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
            180                 185                 190

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
        195                 200                 205

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
    210                 215                 220

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
225                 230                 235                 240

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
                245                 250                 255

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
            260                 265                 270

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
        275                 280                 285

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
    290                 295                 300

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
305                 310                 315                 320

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
                325                 330                 335
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Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
            340                 345                 350

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
        355                 360                 365

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
    370                 375                 380

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
385                 390                 395                 400

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
                405                 410                 415

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
            420                 425                 430

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
        435                 440                 445

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
    450                 455                 460

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
465                 470                 475                 480

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
                485                 490                 495

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
            500                 505                 510

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
        515                 520                 525

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
    530                 535                 540

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
545                 550                 555                 560

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
                565                 570                 575

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
            580                 585                 590

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
        595                 600                 605

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
    610                 615                 620

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
625                 630                 635                 640

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
                645                 650                 655

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
            660                 665                 670

Ala Ala Leu Gly Leu
        675
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<210> 582
<211> 665
<212> PRT
<213> Homo sapiens

<400> 582
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
1 5 10 15

Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu
20 25 30

Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly
35 40 45

Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln
50 55 60

Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
65 70 75 80

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
85 90 95

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
100 105 110

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
115 120 125

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
130 135 140

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
145 150 155 160

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
165 170 175

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
180 185 190

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
195 200 205

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
210 215 220

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
225 230 235 240

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
245 250 255

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
260 265 270

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
275 280 285

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
290 295 300

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
305 310 315 320

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
325 330 335

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
340 345 350

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
355 360 365

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
370 375 380

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
385 390 395 400

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
405 410 415

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
420 425 430

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
435 440 445

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
450 455 460

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
465 470 475 480

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
485 490 495

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
500 505 510

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
515 520 525

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
530 535 540

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
545 550 555 560

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
565 570 575

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
580 585 590

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
595 600 605

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
610 615 620

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
625 630 635 640

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
645 650 655

Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 583
<211> 733

<212> PRT
<213> Homo sapiens

<400> 583
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1 5 10 15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
20 25 30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
35 40 45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50 55 60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65 70 75 80

Ser Leu Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly Ser His Leu
85 90 95

Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr
100 105 110

Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly
115 120 125

Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu
130 135 140

Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
145 150 155 160

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
165 170 175

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
180 185 190

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
195 200 205

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
210 215 220

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
225 230 235 240

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
245 250 255

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
260 265 270

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
275 280 285

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
290 295 300

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
305 310 315 320

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
325 330 335

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln

340 345 350

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
355 360 365

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
370 375 380

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
385 390 395 400

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
405 410 415

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
420 425 430

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
435 440 445

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
450 455 460

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
465 470 475 480

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
485 490 495

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
500 505 510

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
515 520 525

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
530 535 540

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
545 550 555 560

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
565 570 575

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
580 585 590

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
595 600 605

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
610 615 620

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
625 630 635 640

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
645 650 655

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
660 665 670

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
675 680 685

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
690 695 700

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
705 710 715 720

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
725 730

<210> 584
<211> 743
<212> PRT
<213> Homo sapiens

<400> 584
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1 5 10 15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
20 25 30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe
35 40 45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50 55 60

Phe Ile Asn Thr Thr Ile Ala Thr Ile Ala Ala Lys Glu Glu Gly Val
65 70 75 80

Ser Met Ala Lys Arg Glu Glu Ala Glu Ala Glu Ala Glu Pro Lys Phe
85 90 95

Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu
100 105 110

Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr Gly
115 120 125

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys
130 135 140

Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Asp Ala
145 150 155 160

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
165 170 175

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
180 185 190

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
195 200 205

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
210 215 220

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
225 230 235 240

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
245 250 255

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
260 265 270

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
275 280 285

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His

290 295 300

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
305 310 315 320

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
325 330 335

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
340 345 350

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
355 360 365

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
370 375 380

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
385 390 395 400

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
405 410 415

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
420 425 430

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
435 440 445

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
450 455 460

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
465 470 475 480

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
485 490 495

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
500 505 510

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
515 520 525

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
530 535 540

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
545 550 555 560

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
565 570 575

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
580 585 590

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
595 600 605

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
610 615 620

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
625 630 635 640

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
645 650 655

```
Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
            660                 665                 670

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
        675                 680                 685

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
    690                 695                 700

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
705                 710                 715                 720

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
                725                 730                 735

Ser Gln Ala Ala Leu Gly Leu
            740


<210> 585
<211> 672
<212> PRT
<213> Homo sapiens

<400> 585
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly
             20                  25                  30

Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe
         35                  40                  45

Phe Tyr Thr Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro
     50                  55                  60

Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr
 65                  70                  75                  80

Gln Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His
                 85                  90                  95

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
            100                 105                 110

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
        115                 120                 125

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
    130                 135                 140

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
145                 150                 155                 160

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
                165                 170                 175

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
            180                 185                 190

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
        195                 200                 205

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
    210                 215                 220

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
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225 230 235 240

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
245 250 255

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
260 265 270

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
275 280 285

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
290 295 300

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
305 310 315 320

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
325 330 335

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
340 345 350

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
355 360 365

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
370 375 380

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
385 390 395 400

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
405 410 415

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
420 425 430

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
435 440 445

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
450 455 460

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
465 470 475 480

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
485 490 495

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
500 505 510

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
515 520 525

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
530 535 540

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
545 550 555 560

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
565 570 575

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
580 585 590

```
Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
        595                 600                 605

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
    610                 615                 620

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
625                 630                 635                 640

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
                645                 650                 655

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665                 670


<210> 586
<211> 671
<212> PRT
<213> Homo sapiens

<400> 586
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Phe Val Asn Gln His Leu Cys Gly
            20                  25                  30

Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe
        35                  40                  45

Phe Tyr Thr Pro Lys Thr Lys Arg Gly Gly Gly Pro Gly Arg Gly Lys
    50                  55                  60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65                  70                  75                  80

Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg
                85                  90                  95

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
            100                 105                 110

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
        115                 120                 125

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
    130                 135                 140

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
145                 150                 155                 160

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
                165                 170                 175

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
            180                 185                 190

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
        195                 200                 205

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
    210                 215                 220

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
225                 230                 235                 240

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
```

245 250 255

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
260 265 270

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
275 280 285

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
290 295 300

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
305 310 315 320

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
325 330 335

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
340 345 350

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
355 360 365

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
370 375 380

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
385 390 395 400

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
405 410 415

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
420 425 430

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
435 440 445

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
450 455 460

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
465 470 475 480

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
485 490 495

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
500 505 510

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
515 520 525

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
530 535 540

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
545 550 555 560

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
565 570 575

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
580 585 590

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
595 600 605

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
610 615 620

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
625 630 635 640

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
645 650 655

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 587
<211> 794
<212> PRT
<213> Homo sapiens

<400> 587
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Pro Arg Ala Gly Arg Arg Pro
20 25 30

Ala Arg Pro Arg Gly Cys Ala Asp Arg Pro Glu Glu Leu Leu Glu Gln
35 40 45

Leu Tyr Gly Arg Leu Ala Ala Gly Val Leu Ser Ala Phe His His Thr
50 55 60

Leu Gln Leu Gly Pro Arg Glu Gln Ala Arg Asn Ala Ser Cys Pro Ala
65 70 75 80

Gly Gly Arg Pro Ala Asp Arg Arg Phe Arg Pro Pro Thr Asn Leu Arg
85 90 95

Ser Val Ser Pro Trp Ala Tyr Arg Ile Ser Tyr Asp Pro Ala Arg Tyr
100 105 110

Pro Arg Tyr Leu Pro Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu Thr
115 120 125

Gly Leu Phe Gly Glu Glu Asp Val Arg Phe Arg Ser Ala Pro Val Tyr
130 135 140

Met Pro Thr Val Val Leu Arg Arg Thr Pro Ala Cys Ala Gly Gly Arg
145 150 155 160

Ser Val Tyr Thr Glu Ala Tyr Val Thr Ile Pro Val Gly Cys Thr Cys
165 170 175

Val Pro Glu Pro Glu Lys Asp Ala Asp Ser Ile Asn Ser Ser Ile Asp
180 185 190

Lys Gln Gly Ala Lys Leu Leu Leu Gly Pro Asn Asp Ala Pro Ala Gly
195 200 205

Pro Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
210 215 220

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
225 230 235 240

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
245 250 255

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
260 265 270

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
275 280 285

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
290 295 300

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
305 310 315 320

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
325 330 335

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
340 345 350

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
355 360 365

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
370 375 380

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
385 390 395 400

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
405 410 415

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
420 425 430

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
435 440 445

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
450 455 460

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
465 470 475 480

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
485 490 495

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
500 505 510

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
515 520 525

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
530 535 540

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
545 550 555 560

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
565 570 575

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
580 585 590

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
595 600 605

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
610 615 620

```
Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
625                 630                 635                 640

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
                645                 650                 655

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
            660                 665                 670

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
        675                 680                 685

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
    690                 695                 700

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
705                 710                 715                 720

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
                725                 730                 735

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
            740                 745                 750

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
        755                 760                 765

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
    770                 775                 780

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
785                 790
```

<210> 588
<211> 623
<212> PRT
<213> Homo sapiens

```
<400> 588
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Gly Cys Lys Asn Phe Phe Trp
             20                  25                  30

Lys Thr Phe Thr Ser Cys Asp Ala His Lys Ser Glu Val Ala His Arg
         35                  40                  45

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
     50                  55                  60

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
 65                  70                  75                  80

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
                 85                  90                  95

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
            100                 105                 110

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
        115                 120                 125

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
    130                 135                 140
```

```
Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
145                 150                 155                 160

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
                165                 170                 175

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
            180                 185                 190

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
        195                 200                 205

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
    210                 215                 220

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
225                 230                 235                 240

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
                245                 250                 255

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
            260                 265                 270

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
        275                 280                 285

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
    290                 295                 300

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
305                 310                 315                 320

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
                325                 330                 335

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
            340                 345                 350

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
        355                 360                 365

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
    370                 375                 380

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
385                 390                 395                 400

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
                405                 410                 415

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
            420                 425                 430

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
        435                 440                 445

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
    450                 455                 460

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
465                 470                 475                 480

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
                485                 490                 495

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
```

```
            500                 505                 510
Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
        515                 520                 525
Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
    530                 535                 540
Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
545                 550                 555                 560
Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
                565                 570                 575
Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
            580                 585                 590
Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
        595                 600                 605
Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
    610                 615                 620
```

<210> 589
<211> 794
<212> PRT
<213> Homo sapiens

<400> 589

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15
Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30
His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60
Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95
Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160
Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190
Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
```

```
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560
```

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Pro Arg Ala Gly Arg Arg Pro Ala Arg Pro Arg Gly Cys Ala
610 615 620

Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu Ala Ala
625 630 635 640

Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro Arg Glu
645 650 655

Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala Asp Arg
660 665 670

Arg Phe Arg Pro Pro Thr Asn Leu Arg Ser Val Ser Pro Trp Ala Tyr
675 680 685

Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro Glu Ala
690 695 700

Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu Glu Asp
705 710 715 720

Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val Leu Arg
725 730 735

Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu Ala Tyr
740 745 750

Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu Lys Asp
755 760 765

Ala Asp Ser Ile Asn Ser Ser Ile Asp Lys Gln Gly Ala Lys Leu Leu
770 775 780

Leu Gly Pro Asn Asp Ala Pro Ala Gly Pro
785 790

<210> 590
<211> 838
<212> PRT
<213> Homo sapiens

<400> 590
Met Lys Leu Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

```
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
```

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu
610 615 620

Ser Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser
625 630 635 640

Leu Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu
645 650 655

Leu Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr
660 665 670

Lys Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp
675 680 685

Ser Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe
690 695 700

Pro Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn
705 710 715 720

Thr Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His
725 730 735

Tyr Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly
740 745 750

Ile Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser
755 760 765

Pro Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp
770 775 780

Ser Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro
785 790 795 800

Ser Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg

805 810 815

Lys Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser
820 825 830

Arg Ser Gln Ser Glu Leu
835

<210> 591
<211> 1015
<212> PRT
<213> Homo sapiens

<400> 591
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile

```
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala
    610                 615                 620

Ala Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys
625                 630                 635                 640
```

```
Ser Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly
                645                 650                 655

Leu Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg
            660                 665                 670

Ser Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala
        675                 680                 685

Cys Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser
    690                 695                 700

Arg Val Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala
705                 710                 715                 720

Gln Asn Ser Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln
                725                 730                 735

Arg His Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln
            740                 745                 750

Phe Gly Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro
        755                 760                 765

Ala Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala
    770                 775                 780

His Asn Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu
785                 790                 795                 800

Phe Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln
                805                 810                 815

Gly Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly
            820                 825                 830

Trp Thr Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg
        835                 840                 845

Pro Trp Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe
    850                 855                 860

Trp Leu Gly Leu Glu Lys Val His Ser Ile Thr Gly Asp Arg Asn Ser
865                 870                 875                 880

Arg Leu Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu
                885                 890                 895

Gln Phe Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln
            900                 905                 910

Leu Thr Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro
        915                 920                 925

Ser Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu
    930                 935                 940

Arg Arg Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe
945                 950                 955                 960

Gly Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile
                965                 970                 975

Pro Gln Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp
            980                 985                 990

Arg Gly Arg Tyr Tyr Pro Leu Gln  Ala Thr Thr Met Leu  Ile Gln Pro
        995                 1000                1005
```

```
Met Ala  Ala Glu Ala Ala Ser
    1010                1015


<210> 592
<211> 767
<212> PRT
<213> Homo sapiens

<400> 592
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300
```

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Met Ala Ser Arg Ser Met Arg Leu Leu Leu Leu Leu Ser Cys Leu
610 615 620

Ala Lys Thr Gly Val Leu Gly Asp Ile Ile Met Arg Pro Ser Cys Ala
625 630 635 640

Pro Gly Trp Phe Tyr His Lys Ser Asn Cys Tyr Gly Tyr Phe Arg Lys
645 650 655

Leu Arg Asn Trp Ser Asp Ala Glu Leu Glu Cys Gln Ser Tyr Gly Asn

660 665 670

Gly Ala His Leu Ala Ser Ile Leu Ser Leu Lys Glu Ala Ser Thr Ile
675 680 685

Ala Glu Tyr Ile Ser Gly Tyr Gln Arg Ser Gln Pro Ile Trp Ile Gly
690 695 700

Leu His Asp Pro Gln Lys Arg Gln Gln Trp Gln Trp Ile Asp Gly Ala
705 710 715 720

Met Tyr Leu Tyr Arg Ser Trp Ser Gly Lys Ser Met Gly Gly Asn Lys
725 730 735

His Cys Ala Glu Met Ser Ser Asn Asn Asn Phe Leu Thr Trp Ser Ser
740 745 750

Asn Glu Cys Asn Lys Arg Gln His Phe Leu Cys Lys Tyr Arg Pro
755 760 765

<210> 593
<211> 669
<212> PRT
<213> Homo sapiens

<400> 593
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu
20 25 30

Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr
35 40 45

Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly
50 55 60

Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu
65 70 75 80

Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
85 90 95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
100 105 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
115 120 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
130 135 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145 150 155 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
165 170 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
180 185 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
195 200 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
210 215 220

```
Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
    370                 375                 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385                 390                 395                 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
                405                 410                 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
            420                 425                 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
        435                 440                 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
    450                 455                 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465                 470                 475                 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
                485                 490                 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
            500                 505                 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
        515                 520                 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
    530                 535                 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545                 550                 555                 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
                565                 570                 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
```

```
            580                 585                 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
        595                 600                 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
    610                 615                 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625                 630                 635                 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
                645                 650                 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665
```

<210> 594
<211> 666
<212> PRT
<213> Homo sapiens

<400> 594

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ala Gly Val
  1               5                  10                  15

Ser Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
            20                  25                  30

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
        35                  40                  45

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
    50                  55                  60

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
65                  70                  75                  80

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                85                  90                  95

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            100                 105                 110

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        115                 120                 125

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    130                 135                 140

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
145                 150                 155                 160

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                165                 170                 175

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            180                 185                 190

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        195                 200                 205

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    210                 215                 220

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
```

225 230 235 240

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
245 250 255

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
260 265 270

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
275 280 285

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
290 295 300

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
305 310 315 320

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
325 330 335

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
340 345 350

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
355 360 365

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
370 375 380

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
385 390 395 400

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
405 410 415

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
420 425 430

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
435 440 445

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
450 455 460

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
465 470 475 480

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
485 490 495

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
500 505 510

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
515 520 525

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
530 535 540

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
545 550 555 560

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
565 570 575

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
580 585 590

```
Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Phe Val Asn Gln His
        595                 600                 605

Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu
    610                 615                 620

Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg
625                 630                 635                 640

Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
                645                 650                 655

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
            660                 665
```

<210> 595
<211> 719
<212> PRT
<213> Homo sapiens

<400> 595

```
Met Lys Leu Lys Thr Val Arg Ser Ala Val Leu Ser Ser Leu Phe Ala
  1               5                  10                  15

Ser Gln Val Leu Gly Gln Pro Ile Asp Asp Thr Glu Ser Gln Thr Thr
             20                  25                  30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
         35                  40                  45

Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Lys
     50                  55                  60

Arg Glu Glu Gly Glu Pro Lys Phe Val Asn Gln His Leu Cys Gly Ser
 65                  70                  75                  80

His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe
                 85                  90                  95

Tyr Thr Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln
            100                 105                 110

Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
        115                 120                 125

Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg
    130                 135                 140

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
145                 150                 155                 160

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
                165                 170                 175

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
            180                 185                 190

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
        195                 200                 205

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
    210                 215                 220

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
225                 230                 235                 240
```

```
Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                245                 250                 255

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            260                 265                 270

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        275                 280                 285

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    290                 295                 300

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
305                 310                 315                 320

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                325                 330                 335

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            340                 345                 350

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        355                 360                 365

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    370                 375                 380

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
385                 390                 395                 400

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                405                 410                 415

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            420                 425                 430

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        435                 440                 445

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    450                 455                 460

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
465                 470                 475                 480

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                485                 490                 495

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            500                 505                 510

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        515                 520                 525

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    530                 535                 540

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
545                 550                 555                 560

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                565                 570                 575

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            580                 585                 590

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        595                 600                 605
```

```
Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    610                 615                 620

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
625                 630                 635                 640

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                645                 650                 655

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            660                 665                 670

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        675                 680                 685

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    690                 695                 700

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
705                 710                 715
```

<210> 596
<211> 719
<212> PRT
<213> Homo sapiens

<400> 596

```
Met Lys Leu Lys Thr Val Arg Ser Ala Val Leu Ser Ser Leu Phe Ala
  1               5                  10                  15

Ser Gln Val Leu Gly Gln Pro Ile Asp Asp Thr Glu Ser Gln Thr Thr
            20                  25                  30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
        35                  40                  45

Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Lys
    50                  55                  60

Arg Glu Glu Gly Glu Pro Lys Phe Val Asn Gln His Leu Cys Gly Ser
65                  70                  75                  80

His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe
                85                  90                  95

Tyr Thr Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln
            100                 105                 110

Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
        115                 120                 125

Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg
    130                 135                 140

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
145                 150                 155                 160

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
                165                 170                 175

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
            180                 185                 190

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
        195                 200                 205

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
```

```
    210                 215                 220

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
225                 230                 235                 240

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                245                 250                 255

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            260                 265                 270

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        275                 280                 285

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    290                 295                 300

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
305                 310                 315                 320

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                325                 330                 335

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            340                 345                 350

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        355                 360                 365

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    370                 375                 380

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
385                 390                 395                 400

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                405                 410                 415

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            420                 425                 430

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        435                 440                 445

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    450                 455                 460

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
465                 470                 475                 480

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                485                 490                 495

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            500                 505                 510

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        515                 520                 525

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    530                 535                 540

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
545                 550                 555                 560

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                565                 570                 575
```

```
Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            580                 585                 590

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        595                 600                 605

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    610                 615                 620

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
625                 630                 635                 640

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                645                 650                 655

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            660                 665                 670

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        675                 680                 685

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    690                 695                 700

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
705                 710                 715
```

<210> 597
<211> 671
<212> PRT
<213> Homo sapiens

<400> 597

```
Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
  1               5                  10                  15

Ser Val Ile Asn Tyr Lys Arg Phe Val Asn Gln His Leu Cys Gly Ser
            20                  25                  30

His Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe
        35                  40                  45

Tyr Thr Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln
    50                  55                  60

Thr Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65                  70                  75                  80

Leu Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg
                85                  90                  95

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
            100                 105                 110

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
        115                 120                 125

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
    130                 135                 140

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
145                 150                 155                 160

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
                165                 170                 175
```

```
Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
            180                 185                 190

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
        195                 200                 205

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
    210                 215                 220

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
225                 230                 235                 240

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
                245                 250                 255

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
            260                 265                 270

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
        275                 280                 285

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
    290                 295                 300

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
305                 310                 315                 320

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
                325                 330                 335

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
            340                 345                 350

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
        355                 360                 365

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
    370                 375                 380

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
385                 390                 395                 400

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
                405                 410                 415

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
            420                 425                 430

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
        435                 440                 445

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
    450                 455                 460

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
465                 470                 475                 480

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
                485                 490                 495

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
            500                 505                 510

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
        515                 520                 525

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
    530                 535                 540
```

```
Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
545                 550                 555                 560

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
                565                 570                 575

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
            580                 585                 590

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
        595                 600                 605

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
    610                 615                 620

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
625                 630                 635                 640

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
                645                 650                 655

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665                 670
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<210> 598
<211> 664
<212> PRT
<213> Homo sapiens

<400> 598

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Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
  1               5                  10                  15

Ile Ser Ala His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr
            20                  25                  30

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly
        35                  40                  45

Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
    50                  55                  60

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Asp
65                  70                  75                  80

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
                85                  90                  95

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
            100                 105                 110

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
        115                 120                 125

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
    130                 135                 140

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
145                 150                 155                 160

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
                165                 170                 175

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
            180                 185                 190
```

```
Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
        195                 200                 205

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
    210                 215                 220

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
225                 230                 235                 240

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
                245                 250                 255

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
            260                 265                 270

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
        275                 280                 285

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
    290                 295                 300

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
305                 310                 315                 320

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
                325                 330                 335

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
            340                 345                 350

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
        355                 360                 365

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
    370                 375                 380

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
385                 390                 395                 400

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
                405                 410                 415

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
            420                 425                 430

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
        435                 440                 445

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
    450                 455                 460

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
465                 470                 475                 480

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
                485                 490                 495

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
            500                 505                 510

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
        515                 520                 525

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
    530                 535                 540

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
```

545 550 555 560

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
565 570 575

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
580 585 590

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
595 600 605

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
610 615 620

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
625 630 635 640

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
645 650 655

Ala Ser Gln Ala Ala Leu Gly Leu
660

<210> 599
<211> 664
<212> PRT
<213> Homo sapiens

<400> 599
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr
20 25 30

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly
35 40 45

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
50 55 60

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Asp
65 70 75 80

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
85 90 95

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
100 105 110

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
115 120 125

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
130 135 140

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
145 150 155 160

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
165 170 175

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
180 185 190

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp

195 200 205

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
210 215 220

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
225 230 235 240

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
245 250 255

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
260 265 270

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
275 280 285

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
290 295 300

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
305 310 315 320

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
325 330 335

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
340 345 350

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
355 360 365

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
370 375 380

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
385 390 395 400

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
405 410 415

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
420 425 430

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
435 440 445

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
450 455 460

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
465 470 475 480

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
485 490 495

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
500 505 510

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
515 520 525

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
530 535 540

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
545 550 555 560

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
565 570 575

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
580 585 590

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
595 600 605

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
610 615 620

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
625 630 635 640

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
645 650 655

Ala Ser Gln Ala Ala Leu Gly Leu
660

<210> 600
<211> 663
<212> PRT
<213> Homo sapiens

<400> 600
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu
20 25 30

Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
35 40 45

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
50 55 60

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Asp Ala
65 70 75 80

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
85 90 95

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
100 105 110

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
115 120 125

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
130 135 140

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
145 150 155 160

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
165 170 175

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
180 185 190

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
195 200 205

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
210 215 220

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
225 230 235 240

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
245 250 255

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
260 265 270

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
275 280 285

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
290 295 300

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
305 310 315 320

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
325 330 335

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
340 345 350

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
355 360 365

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
370 375 380

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
385 390 395 400

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
405 410 415

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
420 425 430

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
435 440 445

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
450 455 460

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
465 470 475 480

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
485 490 495

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
500 505 510

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
515 520 525

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
530 535 540

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
545 550 555 560

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
565 570 575

```
Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
            580                 585                 590

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
        595                 600                 605

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
    610                 615                 620

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
625                 630                 635                 640

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
                645                 650                 655

Ser Gln Ala Ala Leu Gly Leu
            660
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<210> 601
<211> 663
<212> PRT
<213> Homo sapiens

<400> 601

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Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu
            20                  25                  30

Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
        35                  40                  45

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
    50                  55                  60

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Asp Ala
65                  70                  75                  80

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
                85                  90                  95

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
            100                 105                 110

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
        115                 120                 125

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
    130                 135                 140

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
145                 150                 155                 160

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
                165                 170                 175

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
            180                 185                 190

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
        195                 200                 205

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
    210                 215                 220
```

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
225 230 235 240

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
245 250 255

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
260 265 270

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
275 280 285

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
290 295 300

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
305 310 315 320

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
325 330 335

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
340 345 350

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
355 360 365

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
370 375 380

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
385 390 395 400

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
405 410 415

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
420 425 430

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
435 440 445

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
450 455 460

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
465 470 475 480

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
485 490 495

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
500 505 510

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
515 520 525

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
530 535 540

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
545 550 555 560

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
565 570 575

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys

580 585 590

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
595 600 605

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
610 615 620

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
625 630 635 640

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
645 650 655

Ser Gln Ala Ala Leu Gly Leu
660

<210> 602
<211> 747
<212> PRT
<213> Homo sapiens

<400> 602
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

```
Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
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595 600 605

Leu Asp Gly Pro Phe Pro Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser
610 615 620

His Val Val Glu Asn Thr Ala Phe Phe Gly Asp Val Val Leu Arg Phe
625 630 635 640

Pro Arg Ile Val His Tyr Tyr Phe Asp His Asn Ser Asn Trp Asn Leu
645 650 655

Leu Ile Arg Trp Gly Ile Ser Phe Cys Asn Gln Thr Gly Val Phe Asn
660 665 670

Gln Gly Pro His Ser Pro Ile Leu Ser Leu Met Ala Gln Glu Leu Gly
675 680 685

Ile Ser Glu Lys Asp Ser Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg
690 695 700

Thr Glu Phe Ile Pro Ser Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu
705 710 715 720

Glu Glu Lys Arg Arg Lys Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys
725 730 735

Gly Pro Arg Ile Ser Arg Ser Gln Ser Glu Leu
740 745

<210> 603
<211> 819
<212> PRT
<213> Homo sapiens

<400> 603
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro

```
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525
```

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu Glu Ile
610 615 620

Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu Ala Leu
625 630 635 640

Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys Ile Leu
645 650 655

Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser Arg Thr
660 665 670

Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro Gln Asp
675 680 685

Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr Ala Phe
690 695 700

Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr Tyr Phe
705 710 715 720

Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile Ser Phe
725 730 735

Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro Ile Leu
740 745 750

Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser Asn Phe
755 760 765

Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser Thr Asp
770 775 780

Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys Lys Glu
785 790 795 800

Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg Ser Gln
805 810 815

Ser Glu Leu

<210> 604
<211> 747
<212> PRT
<213> Homo sapiens

<400> 604
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu

385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Asp Gly Pro Phe Pro Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser
610 615 620

His Val Val Glu Asn Thr Ala Phe Phe Gly Asp Val Val Leu Arg Phe
625 630 635 640

Pro Arg Ile Val His Tyr Tyr Phe Asp His Asn Ser Asn Trp Asn Leu
645 650 655

Leu Ile Arg Trp Gly Ile Ser Phe Cys Asn Gln Thr Gly Val Phe Asn
660 665 670

Gln Gly Pro His Ser Pro Ile Leu Ser Leu Met Ala Gln Glu Leu Gly
675 680 685

Ile Ser Glu Lys Asp Ser Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg
690 695 700

Thr Glu Phe Ile Pro Ser Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu
705 710 715 720

Glu Glu Lys Arg Arg Lys Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys
725 730 735

Gly Pro Arg Ile Ser Arg Ser Gln Ser Glu Leu
740 745

<210> 605
<211> 819
<212> PRT
<213> Homo sapiens

<400> 605
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu Glu Ile
610 615 620

Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu Ala Leu
625 630 635 640

Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys Ile Leu
645 650 655

Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser Arg Thr
660 665 670

Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro Gln Asp
675 680 685

```
Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr Ala Phe
    690                 695                 700

Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr Tyr Phe
705                 710                 715                 720

Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile Ser Phe
                725                 730                 735

Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro Ile Leu
            740                 745                 750

Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser Asn Phe
        755                 760                 765

Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser Thr Asp
    770                 775                 780

Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys Lys Glu
785                 790                 795                 800

Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg Ser Gln
                805                 810                 815

Ser Glu Leu
```

<210> 606
<211> 753
<212> PRT
<213> Homo sapiens

<400> 606

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175
```

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu

```
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg Ser Ala Phe
    610                 615                 620

Ser Val Gly Leu Glu Thr Tyr Val Thr Ile Pro Asn Met Pro Ile Arg
625                 630                 635                 640

Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp Gly Ser Thr
                645                 650                 655

Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe Ala Tyr His
            660                 665                 670

Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe Lys Lys Asp
        675                 680                 685

Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn Asn Val Asp
    690                 695                 700

Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly Asp Gln Val
705                 710                 715                 720

Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu Tyr Ala Asp
                725                 730                 735

Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr His Asp Thr
            740                 745                 750

Asn
```

<210> 607
<211> 753
<212> PRT
<213> Homo sapiens

```
<400> 607
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
```

```
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
```

```
Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg Ser Ala Phe
    610                 615                 620

Ser Val Gly Leu Glu Thr Asn Val Thr Ile Pro Asn Met Pro Ile Arg
625                 630                 635                 640

Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp Gly Ser Thr
                645                 650                 655

Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe Ala Tyr His
            660                 665                 670

Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe Lys Lys Asp
        675                 680                 685

Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn Asn Val Asp
    690                 695                 700

Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly Asp Gln Val
705                 710                 715                 720

Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu Tyr Ala Asp
                725                 730                 735

Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr His Asp Thr
            740                 745                 750

Asn
```

<210> 608
<211> 836
<212> PRT
<213> Homo sapiens

<400> 608

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
 1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
```

```
Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Gln Glu Thr Thr Thr Gln Gly Pro Gly Val Leu Leu Pro Leu Pro
    610                 615                 620

Lys Gly Ala Cys Thr Gly Trp Met Ala Gly Ile Pro Gly His Pro Gly
625                 630                 635                 640

His Asn Gly Ala Pro Gly Arg Asp Gly Arg Asp Gly Thr Pro Gly Glu
                645                 650                 655

Lys Gly Glu Lys Gly Asp Pro Gly Leu Ile Gly Pro Lys Gly Asp Ile
            660                 665                 670

Gly Glu Thr Gly Val Pro Gly Ala Glu Gly Pro Arg Gly Phe Pro Gly
        675                 680                 685

Ile Gln Gly Arg Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg
    690                 695                 700

Ser Ala Phe Ser Val Gly Leu Glu Thr Tyr Val Thr Ile Pro Asn Met
705                 710                 715                 720

Pro Ile Arg Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp
```

```
                725                 730                 735

Gly Ser Thr Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe
            740                 745                 750

Ala Tyr His Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe
        755                 760                 765

Lys Lys Asp Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn
    770                 775                 780

Asn Val Asp Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly
785                 790                 795                 800

Asp Gln Val Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu
                805                 810                 815

Tyr Ala Asp Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr
            820                 825                 830

His Asp Thr Asn
        835
```

<210> 609
<211> 668
<212> PRT
<213> Homo sapiens

<400> 609

```
Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
  1               5                  10                  15

Ser Val Ile Asn Tyr Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp
            20                  25                  30

Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp
        35                  40                  45

Leu Val Lys Gly Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser
    50                  55                  60

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
65                  70                  75                  80

Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
                85                  90                  95

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
            100                 105                 110

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
        115                 120                 125

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
    130                 135                 140

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
145                 150                 155                 160

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
                165                 170                 175

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
            180                 185                 190

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
        195                 200                 205
```

```
Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
    210                 215                 220

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
225                 230                 235                 240

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
                245                 250                 255

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
            260                 265                 270

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
        275                 280                 285

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
    290                 295                 300

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
305                 310                 315                 320

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
                325                 330                 335

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
            340                 345                 350

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
        355                 360                 365

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
    370                 375                 380

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
385                 390                 395                 400

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
                405                 410                 415

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
            420                 425                 430

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
        435                 440                 445

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
    450                 455                 460

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
465                 470                 475                 480

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
                485                 490                 495

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
            500                 505                 510

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
        515                 520                 525

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
    530                 535                 540

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
545                 550                 555                 560

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
```

565 570 575

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
580 585 590

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
595 600 605

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
610 615 620

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
625 630 635 640

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
645 650 655

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 610
<211> 730
<212> PRT
<213> Homo sapiens

<400> 610
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1 5 10 15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
20 25 30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
35 40 45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50 55 60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65 70 75 80

Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser
85 90 95

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
100 105 110

Lys Gly Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr
115 120 125

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly
130 135 140

Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
145 150 155 160

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
165 170 175

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
180 185 190

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
195 200 205

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr

```
    210                 215                 220

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
225                 230                 235                 240

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
                245                 250                 255

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
            260                 265                 270

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
        275                 280                 285

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
    290                 295                 300

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
305                 310                 315                 320

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
                325                 330                 335

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
            340                 345                 350

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
        355                 360                 365

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
    370                 375                 380

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
385                 390                 395                 400

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
                405                 410                 415

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
            420                 425                 430

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
        435                 440                 445

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
    450                 455                 460

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
465                 470                 475                 480

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
                485                 490                 495

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
            500                 505                 510

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
        515                 520                 525

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
    530                 535                 540

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
545                 550                 555                 560

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
                565                 570                 575
```

```
Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
          580                 585                 590

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
        595                 600                 605

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
    610                 615                 620

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
625                 630                 635                 640

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
                645                 650                 655

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
            660                 665                 670

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
        675                 680                 685

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
    690                 695                 700

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
705                 710                 715                 720

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                725                 730
```

<210> 611
<211> 662
<212> PRT
<213> Homo sapiens

<400> 611

```
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
  1               5                  10                  15

Ala His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
             20                  25                  30

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His
         35                  40                  45

Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
     50                  55                  60

Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Asp Ala His
 65                  70                  75                  80

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
                 85                  90                  95

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
            100                 105                 110

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
        115                 120                 125

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
    130                 135                 140

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
145                 150                 155                 160
```

```
Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
                165                 170                 175

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
            180                 185                 190

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
        195                 200                 205

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
    210                 215                 220

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
225                 230                 235                 240

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
                245                 250                 255

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
            260                 265                 270

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
        275                 280                 285

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
    290                 295                 300

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
305                 310                 315                 320

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
                325                 330                 335

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
            340                 345                 350

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
        355                 360                 365

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
    370                 375                 380

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
385                 390                 395                 400

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
                405                 410                 415

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
            420                 425                 430

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
        435                 440                 445

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
    450                 455                 460

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
465                 470                 475                 480

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
                485                 490                 495

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
            500                 505                 510

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
        515                 520                 525
```

```
Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
    530                 535                 540

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
545                 550                 555                 560

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
                565                 570                 575

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
            580                 585                 590

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
        595                 600                 605

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
    610                 615                 620

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
625                 630                 635                 640

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
                645                 650                 655

Gln Ala Ala Leu Gly Leu
            660
```

<210> 612
<211> 730
<212> PRT
<213> Homo sapiens

<400> 612

```
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
  1               5                  10                  15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
            20                  25                  30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
        35                  40                  45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
    50                  55                  60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65                  70                  75                  80

Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser
                85                  90                  95

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
            100                 105                 110

Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr
        115                 120                 125

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly
    130                 135                 140

Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
145                 150                 155                 160

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
                165                 170                 175
```

```
Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
            180                 185                 190

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
        195                 200                 205

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
    210                 215                 220

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
225                 230                 235                 240

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
                245                 250                 255

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
            260                 265                 270

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
        275                 280                 285

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
    290                 295                 300

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
305                 310                 315                 320

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
                325                 330                 335

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
            340                 345                 350

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
        355                 360                 365

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
    370                 375                 380

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
385                 390                 395                 400

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
                405                 410                 415

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
            420                 425                 430

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
        435                 440                 445

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
    450                 455                 460

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
465                 470                 475                 480

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
                485                 490                 495

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
            500                 505                 510

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
        515                 520                 525

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
```

530 535 540

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
545 550 555 560

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
565 570 575

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
580 585 590

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
595 600 605

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
610 615 620

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
625 630 635 640

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
645 650 655

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
660 665 670

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
675 680 685

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
690 695 700

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
705 710 715 720

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
725 730

<210> 613
<211> 668
<212> PRT
<213> Homo sapiens

<400> 613
Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
1 5 10 15

Ser Val Ile Asn Tyr Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp
20 25 30

Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp
35 40 45

Leu Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser
50 55 60

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
65 70 75 80

Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
85 90 95

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
100 105 110

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu

```
        115                 120                 125

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
    130                 135                 140

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
145                 150                 155                 160

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
                165                 170                 175

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
            180                 185                 190

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
        195                 200                 205

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
    210                 215                 220

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
225                 230                 235                 240

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
                245                 250                 255

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
            260                 265                 270

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
        275                 280                 285

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
    290                 295                 300

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
305                 310                 315                 320

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
                325                 330                 335

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
            340                 345                 350

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
        355                 360                 365

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
    370                 375                 380

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
385                 390                 395                 400

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
                405                 410                 415

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
            420                 425                 430

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
        435                 440                 445

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
    450                 455                 460

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
465                 470                 475                 480
```

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
485 490 495

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
500 505 510

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
515 520 525

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
530 535 540

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
545 550 555 560

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
565 570 575

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
580 585 590

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
595 600 605

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
610 615 620

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
625 630 635 640

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
645 650 655

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 614
<211> 662
<212> PRT
<213> Homo sapiens

<400> 614
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
1 5 10 15

Ala His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
20 25 30

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His
35 40 45

Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
50 55 60

Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Asp Ala His
65 70 75 80

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
85 90 95

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
100 105 110

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
115 120 125

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
130 135 140

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
145 150 155 160

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
165 170 175

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
180 185 190

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
195 200 205

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
210 215 220

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
225 230 235 240

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
245 250 255

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
260 265 270

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
275 280 285

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
290 295 300

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
305 310 315 320

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
325 330 335

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
340 345 350

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
355 360 365

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
370 375 380

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
385 390 395 400

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
405 410 415

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
420 425 430

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
435 440 445

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
450 455 460

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
465 470 475 480

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
485 490 495

```
Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
            500                 505                 510

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
        515                 520                 525

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
    530                 535                 540

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
545                 550                 555                 560

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
                565                 570                 575

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
            580                 585                 590

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
        595                 600                 605

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
    610                 615                 620

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
625                 630                 635                 640

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
                645                 650                 655

Gln Ala Ala Leu Gly Leu
            660
```

<210> 615
<211> 640
<212> PRT
<213> Homo sapiens

<400> 615

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140
```

```
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
```

```
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly
    610                 615                 620

Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln
625                 630                 635                 640
```

<210> 616
<211> 740
<212> PRT
<213> Homo sapiens

<400> 616

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
             20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
         35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
     50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
 65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                 85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
```

```
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540
```

```
Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Val Pro Ala Pro Lys Val Pro Ile Lys Met Gln Val Lys His Trp
    610                 615                 620

Pro Ser Glu Gln Asp Pro Glu Lys Ala Trp Gly Ala Arg Val Val Glu
625                 630                 635                 640

Pro Pro Glu Lys Asp Asp Gln Leu Val Val Leu Phe Pro Val Gln Lys
                645                 650                 655

Pro Lys Leu Leu Thr Thr Glu Glu Lys Pro Arg Gly Gln Gly Arg Gly
            660                 665                 670

Pro Ile Leu Pro Gly Thr Lys Ala Trp Met Glu Thr Glu Asp Thr Leu
        675                 680                 685

Gly Arg Val Leu Ser Pro Glu Pro Asp His Asp Ser Leu Tyr His Pro
    690                 695                 700

Pro Pro Glu Glu Asp Gln Gly Glu Glu Arg Pro Arg Leu Trp Val Met
705                 710                 715                 720

Pro Asn His Gln Val Leu Leu Gly Pro Glu Glu Asp Gln Asp His Ile
                725                 730                 735

Tyr His Pro Gln
            740
```

<210> 617
<211> 645
<212> PRT
<213> Homo sapiens

<400> 617

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1                 5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110
```

```
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480
```

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
610 615 620

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
625 630 635 640

Thr Arg Gln Arg Tyr
645

<210> 618
<211> 643
<212> PRT
<213> Homo sapiens

<400> 618
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

```
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
```

```
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
    610                 615                 620

Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
625                 630                 635                 640

Gln Arg Tyr
```

<210> 619
<211> 643
<212> PRT
<213> Homo sapiens

<400> 619

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Ile Lys Pro Glu Ala Pro Gly Glu
             20                  25                  30

Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
         35                  40                  45

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Asp Ala His Lys Ser Glu
     50                  55                  60

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
 65                  70                  75                  80

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
                 85                  90                  95

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
            100                 105                 110

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
        115                 120                 125

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
    130                 135                 140

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
145                 150                 155                 160

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
```

```
                165                 170                 175

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
            180                 185                 190

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
        195                 200                 205

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
    210                 215                 220

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
225                 230                 235                 240

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
                245                 250                 255

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
            260                 265                 270

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
        275                 280                 285

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
    290                 295                 300

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
305                 310                 315                 320

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
                325                 330                 335

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
            340                 345                 350

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
        355                 360                 365

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
    370                 375                 380

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
385                 390                 395                 400

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
                405                 410                 415

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
            420                 425                 430

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
        435                 440                 445

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
    450                 455                 460

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
465                 470                 475                 480

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
                485                 490                 495

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
            500                 505                 510

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
        515                 520                 525
```

```
Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
    530                 535                 540

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
545                 550                 555                 560

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
                565                 570                 575

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
            580                 585                 590

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
        595                 600                 605

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
    610                 615                 620

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
625                 630                 635                 640

Leu Gly Leu
```

<210> 620
<211> 643
<212> PRT
<213> Homo sapiens

<400> 620

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ile Lys Pro Glu Ala Pro Gly Glu
             20                  25                  30

Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
         35                  40                  45

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Asp Ala His Lys Ser Glu
     50                  55                  60

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
 65                  70                  75                  80

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
                 85                  90                  95

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
            100                 105                 110

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
        115                 120                 125

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
    130                 135                 140

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
145                 150                 155                 160

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
                165                 170                 175

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
            180                 185                 190
```

```
Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
        195                 200                 205

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
    210                 215                 220

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
225                 230                 235                 240

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
                245                 250                 255

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
            260                 265                 270

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
        275                 280                 285

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
    290                 295                 300

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
305                 310                 315                 320

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
                325                 330                 335

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
            340                 345                 350

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
        355                 360                 365

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
    370                 375                 380

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
385                 390                 395                 400

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
                405                 410                 415

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
            420                 425                 430

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
        435                 440                 445

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
    450                 455                 460

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
465                 470                 475                 480

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
                485                 490                 495

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
            500                 505                 510

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
        515                 520                 525

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
    530                 535                 540

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
545                 550                 555                 560
```

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
565 570 575

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
580 585 590

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
595 600 605

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
610 615 620

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
625 630 635 640

Leu Gly Leu

<210> 621
<211> 713
<212> PRT
<213> Homo sapiens

<400> 621
Met Lys Leu Lys Thr Val Arg Ser Ala Val Leu Ser Ser Leu Phe Ala
1 5 10 15

Ser Gln Val Leu Gly Gln Pro Ile Asp Asp Thr Glu Ser Gln Thr Thr
20 25 30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
35 40 45

Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Lys
50 55 60

Arg Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu
65 70 75 80

Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly
85 90 95

Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln
100 105 110

Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
115 120 125

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
130 135 140

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
145 150 155 160

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
165 170 175

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
180 185 190

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
195 200 205

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
210 215 220

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu

225 230 235 240

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
245 250 255

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
260 265 270

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
275 280 285

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
290 295 300

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
305 310 315 320

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
325 330 335

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
340 345 350

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
355 360 365

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
370 375 380

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
385 390 395 400

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
405 410 415

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
420 425 430

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
435 440 445

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
450 455 460

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
465 470 475 480

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
485 490 495

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
500 505 510

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
515 520 525

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
530 535 540

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
545 550 555 560

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
565 570 575

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
580 585 590

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
595 600 605

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
610 615 620

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
625 630 635 640

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
645 650 655

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
660 665 670

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
675 680 685

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
690 695 700

Ala Ala Ser Gln Ala Ala Leu Gly Leu
705 710

<210> 622
<211> 718
<212> PRT
<213> Homo sapiens

<400> 622
Met Lys Leu Lys Thr Val Arg Ser Ala Val Leu Ser Ser Leu Phe Ala
1 5 10 15

Ser Gln Val Leu Gly Gln Pro Ile Asp Asp Thr Glu Ser Gln Thr Thr
20 25 30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
35 40 45

Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Glu
50 55 60

Glu Gly Glu Pro Lys Arg Phe Val Asn Gln His Leu Cys Gly Ser His
65 70 75 80

Leu Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr
85 90 95

Thr Pro Lys Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr
100 105 110

Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu
115 120 125

Glu Asn Tyr Cys Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe
130 135 140

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
145 150 155 160

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
165 170 175

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
180 185 190

```
Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
        195                 200                 205

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
    210                 215                 220

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
225                 230                 235                 240

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
                245                 250                 255

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            260                 265                 270

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        275                 280                 285

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    290                 295                 300

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
305                 310                 315                 320

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                325                 330                 335

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            340                 345                 350

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        355                 360                 365

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    370                 375                 380

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
385                 390                 395                 400

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                405                 410                 415

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            420                 425                 430

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        435                 440                 445

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    450                 455                 460

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
465                 470                 475                 480

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                485                 490                 495

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            500                 505                 510

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        515                 520                 525

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    530                 535                 540

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
545                 550                 555                 560
```

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
565 570 575

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
580 585 590

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
595 600 605

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
610 615 620

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
625 630 635 640

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
645 650 655

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
660 665 670

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
675 680 685

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
690 695 700

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
705 710 715

<210> 623
<211> 655
<212> PRT
<213> Homo sapiens

<400> 623
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser
20 25 30

Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala
35 40 45

Trp Leu Val Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg
50 55 60

Phe Lys Asp Leu Gly Glu Asp Ala His Lys Ser Glu Val Ala His Arg
65 70 75 80

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
85 90 95

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
100 105 110

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
115 120 125

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
130 135 140

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
145 150 155 160

```
Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
                165                 170                 175

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
            180                 185                 190

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
        195                 200                 205

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
    210                 215                 220

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
225                 230                 235                 240

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
                245                 250                 255

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
            260                 265                 270

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
        275                 280                 285

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
    290                 295                 300

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
305                 310                 315                 320

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
                325                 330                 335

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
            340                 345                 350

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
        355                 360                 365

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
    370                 375                 380

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
385                 390                 395                 400

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
                405                 410                 415

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
            420                 425                 430

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
        435                 440                 445

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
    450                 455                 460

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
465                 470                 475                 480

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
                485                 490                 495

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
            500                 505                 510

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
```

```
        515                 520                 525

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
    530                 535                 540

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
545                 550                 555                 560

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
                565                 570                 575

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
            580                 585                 590

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
        595                 600                 605

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
    610                 615                 620

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
625                 630                 635                 640

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                645                 650                 655
```

<210> 624
<211> 970
<212> PRT
<213> Homo sapiens

<400> 624

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asn Glu Ile Leu Gly Leu Lys Leu
            20                  25                  30

Pro Gly Glu Pro Pro Leu Thr Ala Asn Thr Val Cys Leu Thr Leu Ser
        35                  40                  45

Gly Leu Ser Lys Arg Gln Leu Asp Leu Cys Leu Arg Asn Pro Asp Val
    50                  55                  60

Thr Ala Ser Ala Leu Gln Gly Leu His Ile Ala Val His Glu Cys Gln
65                  70                  75                  80

His Gln Leu Arg Asp Gln Arg Trp Asn Cys Ser Ala Leu Glu Gly Gly
                85                  90                  95

Gly Arg Leu Pro His His Ser Ala Ile Leu Lys Arg Gly Phe Arg Glu
            100                 105                 110

Ser Ala Phe Ser Phe Ser Met Leu Ala Ala Gly Val Met His Ala Val
        115                 120                 125

Ala Thr Ala Cys Ser Leu Gly Lys Leu Val Ser Cys Gly Cys Gly Trp
    130                 135                 140

Lys Gly Ser Gly Glu Gln Asp Arg Leu Arg Ala Lys Leu Leu Gln Leu
145                 150                 155                 160

Gln Ala Leu Ser Arg Gly Lys Ser Phe Pro His Ser Leu Pro Ser Pro
                165                 170                 175

Gly Pro Gly Ser Ser Pro Ser Pro Gly Pro Gln Asp Thr Trp Glu Trp
```

```
            180                 185                 190

Gly Gly Cys Asn His Asp Met Asp Phe Gly Glu Lys Phe Ser Arg Asp
        195                 200                 205

Phe Leu Asp Ser Arg Glu Ala Pro Arg Asp Ile Gln Ala Arg Met Arg
    210                 215                 220

Ile His Asn Asn Arg Val Gly Arg Gln Val Val Thr Glu Asn Leu Lys
225                 230                 235                 240

Arg Lys Cys Lys Cys His Gly Thr Ser Gly Ser Cys Gln Phe Lys Thr
                245                 250                 255

Cys Trp Arg Ala Ala Pro Glu Phe Arg Ala Val Gly Ala Ala Leu Arg
            260                 265                 270

Glu Arg Leu Gly Arg Ala Ile Phe Ile Asp Thr His Asn Arg Asn Ser
        275                 280                 285

Gly Ala Phe Gln Pro Arg Leu Arg Pro Arg Arg Leu Ser Gly Glu Leu
    290                 295                 300

Val Tyr Phe Glu Lys Ser Pro Asp Phe Cys Glu Arg Asp Pro Thr Met
305                 310                 315                 320

Gly Ser Pro Gly Thr Arg Gly Arg Ala Cys Asn Lys Thr Ser Arg Leu
                325                 330                 335

Leu Asp Gly Cys Gly Ser Leu Cys Cys Gly Arg Gly His Asn Val Leu
            340                 345                 350

Arg Gln Thr Arg Val Glu Arg Cys His Cys Arg Phe His Trp Cys Cys
        355                 360                 365

Tyr Val Leu Cys Asp Glu Cys Lys Val Thr Glu Trp Val Asn Val Cys
    370                 375                 380

Lys Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
385                 390                 395                 400

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
                405                 410                 415

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
            420                 425                 430

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
        435                 440                 445

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
    450                 455                 460

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
465                 470                 475                 480

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
                485                 490                 495

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
            500                 505                 510

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
        515                 520                 525

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
    530                 535                 540
```

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
545 550 555 560

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
565 570 575

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
580 585 590

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
595 600 605

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
610 615 620

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
625 630 635 640

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
645 650 655

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
660 665 670

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
675 680 685

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
690 695 700

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
705 710 715 720

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
725 730 735

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
740 745 750

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
755 760 765

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
770 775 780

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
785 790 795 800

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
805 810 815

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
820 825 830

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
835 840 845

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
850 855 860

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
865 870 875 880

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
885 890 895

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
900 905 910

```
Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
        915                 920                 925

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
    930                 935                 940

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
945                 950                 955                 960

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                965                 970
```

<210> 625
<211> 671
<212> PRT
<213> Homo sapiens

<400> 625

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255
```

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly
610 615 620

Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln
625 630 635 640

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
645 650 655

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln
660 665 670

<210> 626
<211> 664
<212> PRT
<213> Homo sapiens

<400> 626
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu
20 25 30

Val Glu Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr
35 40 45

Pro Lys Thr Glu Ala Glu Asp Leu Gln Val Gly Ile Val Glu Gln Cys
50 55 60

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Asp
65 70 75 80

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
85 90 95

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
100 105 110

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
115 120 125

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
130 135 140

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
145 150 155 160

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
165 170 175

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
180 185 190

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
195 200 205

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
210 215 220

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
225 230 235 240

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
245 250 255

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
260 265 270

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg

```
        275                 280                 285

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
    290                 295                 300

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
305                 310                 315                 320

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
                325                 330                 335

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
            340                 345                 350

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
        355                 360                 365

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
    370                 375                 380

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
385                 390                 395                 400

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
                405                 410                 415

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
            420                 425                 430

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
        435                 440                 445

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
    450                 455                 460

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
465                 470                 475                 480

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
                485                 490                 495

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
            500                 505                 510

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
        515                 520                 525

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
    530                 535                 540

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
545                 550                 555                 560

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
                565                 570                 575

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
            580                 585                 590

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
        595                 600                 605

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
    610                 615                 620

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
625                 630                 635                 640
```

```
Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
                645                 650                 655

Ala Ser Gln Ala Ala Leu Gly Leu
            660
```

<210> 627
<211> 662
<212> PRT
<213> Homo sapiens

<400> 627

```
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
  1               5                  10                  15

Ile Ser Ala Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu
             20                  25                  30

Ala Leu Tyr Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys
         35                  40                  45

Thr Glu Ala Glu Asp Leu Gln Val Gly Ile Val Glu Gln Cys Cys Thr
     50                  55                  60

Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Asp Ala His
 65                  70                  75                  80

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
                 85                  90                  95

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
            100                 105                 110

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
        115                 120                 125

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
    130                 135                 140

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
145                 150                 155                 160

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
                165                 170                 175

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
            180                 185                 190

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
        195                 200                 205

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
    210                 215                 220

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
225                 230                 235                 240

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
                245                 250                 255

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
            260                 265                 270

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
        275                 280                 285
```

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
290 295 300

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
305 310 315 320

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
325 330 335

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
340 345 350

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
355 360 365

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
370 375 380

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
385 390 395 400

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
405 410 415

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
420 425 430

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
435 440 445

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
450 455 460

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
465 470 475 480

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
485 490 495

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
500 505 510

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
515 520 525

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
530 535 540

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
545 550 555 560

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
565 570 575

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
580 585 590

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
595 600 605

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
610 615 620

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
625 630 635 640

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
645 650 655

Gln Ala Ala Leu Gly Leu
660

<210> 628
<211> 657
<212> PRT
<213> Homo sapiens

<400> 628
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Val Pro Ile Tyr Glu Lys Lys Tyr
20 25 30

Gly Gln Val Pro Met Cys Asp Ala Gly Glu Gln Cys Ala Val Arg Lys
35 40 45

Gly Ala Arg Ile Gly Lys Leu Cys Asp Cys Pro Arg Gly Thr Ser Cys
50 55 60

Asn Ser Phe Leu Leu Lys Cys Leu Asp Ala His Lys Ser Glu Val Ala
65 70 75 80

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
85 90 95

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
100 105 110

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
115 120 125

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
130 135 140

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
145 150 155 160

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
165 170 175

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
180 185 190

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
195 200 205

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
210 215 220

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
225 230 235 240

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
245 250 255

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
260 265 270

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
275 280 285

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
290 295 300

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly

305 310 315 320

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
325 330 335

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
340 345 350

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
355 360 365

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
370 375 380

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
385 390 395 400

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
405 410 415

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
420 425 430

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
435 440 445

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
450 455 460

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
465 470 475 480

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
485 490 495

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
500 505 510

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
515 520 525

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
530 535 540

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
545 550 555 560

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
565 570 575

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
580 585 590

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
595 600 605

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
610 615 620

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
625 630 635 640

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
645 650 655

Leu

<210> 629
<211> 740
<212> PRT
<213> Homo sapiens

<400> 629
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Val Pro Ala Pro Lys Val Pro Ile
20 25 30

Lys Met Gln Val Lys His Trp Pro Ser Glu Gln Asp Pro Glu Lys Ala
35 40 45

Trp Gly Ala Arg Val Val Glu Pro Pro Glu Lys Asp Asp Gln Leu Val
50 55 60

Val Leu Phe Pro Val Gln Lys Pro Lys Leu Leu Thr Thr Glu Glu Lys
65 70 75 80

Pro Arg Gly Gln Gly Arg Gly Pro Ile Leu Pro Gly Thr Lys Ala Trp
85 90 95

Met Glu Thr Glu Asp Thr Leu Gly Arg Val Leu Ser Pro Glu Pro Asp
100 105 110

His Asp Ser Leu Tyr His Pro Pro Pro Glu Glu Asp Gln Gly Glu Glu
115 120 125

Arg Pro Arg Leu Trp Val Met Pro Asn His Gln Val Leu Leu Gly Pro
130 135 140

Glu Glu Asp Gln Asp His Ile Tyr His Pro Gln Asp Ala His Lys Ser
145 150 155 160

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
165 170 175

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
180 185 190

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys
195 200 205

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
210 215 220

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly
225 230 235 240

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
245 250 255

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
260 265 270

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
275 280 285

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
290 295 300

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
305 310 315 320

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
325 330 335

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
340 345 350

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
355 360 365

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
370 375 380

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
385 390 395 400

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
405 410 415

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
420 425 430

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
435 440 445

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
450 455 460

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
465 470 475 480

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
485 490 495

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
500 505 510

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
515 520 525

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
530 535 540

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
545 550 555 560

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
565 570 575

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
580 585 590

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
595 600 605

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
610 615 620

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
625 630 635 640

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
645 650 655

Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
660 665 670

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
675 680 685

```
Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
    690                 695                 700

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
705                 710                 715                 720

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
                725                 730                 735

Ala Leu Gly Leu
            740
```

<210> 630
<211> 677
<212> PRT
<213> Homo sapiens

<400> 630

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
  1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ile Lys Pro Glu Ala Pro Gly Glu
            20                  25                  30

Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
        35                  40                  45

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Ile Lys Pro Glu Ala Pro
    50                  55                  60

Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu
65                  70                  75                  80

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Asp Ala His Lys
                85                  90                  95

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
            100                 105                 110

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
        115                 120                 125

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
    130                 135                 140

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
145                 150                 155                 160

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
                165                 170                 175

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
            180                 185                 190

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
        195                 200                 205

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
    210                 215                 220

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
225                 230                 235                 240

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
                245                 250                 255
```

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
260 265 270

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
275 280 285

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
290 295 300

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
305 310 315 320

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
325 330 335

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
340 345 350

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
355 360 365

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
370 375 380

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
385 390 395 400

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
405 410 415

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
420 425 430

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
435 440 445

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
450 455 460

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
465 470 475 480

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
485 490 495

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
500 505 510

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
515 520 525

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
530 535 540

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
545 550 555 560

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
565 570 575

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
580 585 590

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
595 600 605

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu

610 615 620

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
625 630 635 640

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
645 650 655

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
660 665 670

Ala Ala Leu Gly Leu
675

<210> 631
<211> 677
<212> PRT
<213> Homo sapiens

<400> 631
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu

610 615 620

Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
625 630 635 640

Gln Arg Tyr Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
645 650 655

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
660 665 670

Thr Arg Gln Arg Tyr
675

<210> 632
<211> 187
<212> PRT
<213> Homo sapiens

<400> 632
Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
1 5 10 15

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
20 25 30

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
35 40 45

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
50 55 60

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
65 70 75 80

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
85 90 95

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
100 105 110

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
115 120 125

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
130 135 140

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
145 150 155 160

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
165 170 175

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn
180 185

<210> 633
<211> 429
<212> PRT
<213> Homo sapiens

<400> 633
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
1 5 10 15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
20 25 30

```
Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
     50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
 65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
```

385 390 395 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
420 425

<210> 634
<211> 429
<212> PRT
<213> Homo sapiens

<400> 634
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
1 5 10 15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
20 25 30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
35 40 45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
50 55 60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65 70 75 80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
85 90 95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
100 105 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
115 120 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
130 135 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145 150 155 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
165 170 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
180 185 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
195 200 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
210 215 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225 230 235 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
245 250 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
260 265 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser

```
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425
```

<210> 635
<211> 429
<212> PRT
<213> Homo sapiens

<400> 635

```
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
            20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
        35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
    50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
```

```
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425
```

<210> 636
<211> 429
<212> PRT
<213> Homo sapiens

<400> 636

```
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
             20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
         35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
```

```
     50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
 65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415
```

```
His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
           420                 425


<210> 637
<211> 429
<212> PRT
<213> Homo sapiens

<400> 637
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
             20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
         35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
     50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
 65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                 85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190

Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300
```

```
Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425
```

<210> 638
<211> 429
<212> PRT
<213> Homo sapiens

```
<400> 638
Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
  1               5                  10                  15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
             20                  25                  30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
         35                  40                  45

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
     50                  55                  60

Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
 65                  70                  75                  80

Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
                 85                  90                  95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
            100                 105                 110

Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
        115                 120                 125

Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
    130                 135                 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
145                 150                 155                 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
                165                 170                 175

Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
            180                 185                 190
```

```
Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
        195                 200                 205

Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
    210                 215                 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225                 230                 235                 240

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
                245                 250                 255

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
            260                 265                 270

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
        275                 280                 285

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
    290                 295                 300

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305                 310                 315                 320

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
                325                 330                 335

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
            340                 345                 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
        355                 360                 365

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
    370                 375                 380

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385                 390                 395                 400

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
                405                 410                 415

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
            420                 425


<210> 639
<211> 62
<212> PRT
<213> Homo sapiens

<400> 639
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
  1               5                  10                  15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Lys Arg
             20                  25                  30

Gly Gly Gly Pro Gly Arg Gly Lys Arg Gly Ile Val Glu Gln Cys Cys
         35                  40                  45

Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
     50                  55                  60


<210> 640
<211> 62
<212> PRT
```

<213> Homo sapiens

<400> 640
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Lys Arg
20 25 30

Gly Gly Gly Pro Gly Arg Gly Lys Arg Gly Ile Val Glu Gln Cys Cys
35 40 45

Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 641
<211> 58
<212> PRT
<213> Homo sapiens

<400> 641
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Gly
20 25 30

Gly Pro Gly Lys Lys Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55

<210> 642
<211> 58
<212> PRT
<213> Homo sapiens

<400> 642
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Gly
20 25 30

Gly Pro Gly Lys Lys Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55

<210> 643
<211> 63
<212> PRT
<213> Homo sapiens

<400> 643
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 644
<211> 63
<212> PRT
<213> Homo sapiens

<400> 644
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 645
<211> 63
<212> PRT
<213> Homo sapiens

<400> 645
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 646
<211> 58
<212> PRT
<213> Homo sapiens

<400> 646
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Gly
20 25 30

Gly Pro Gly Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55

<210> 647
<211> 166

<212> PRT
<213> Homo sapiens

<400> 647
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 648
<211> 166
<212> PRT
<213> Homo sapiens

<400> 648
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 649
<211> 166
<212> PRT
<213> Homo sapiens

<400> 649
Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 650
<211> 14
<212> PRT
<213> Homo sapiens

<400> 650
Ala Gly Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10

<210> 651
<211> 180
<212> PRT
<213> Homo sapiens

<400> 651

```
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
 1               5                  10                  15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
            20                  25                  30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
        35                  40                  45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
    50                  55                  60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65                  70                  75                  80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
                85                  90                  95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
            100                 105                 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
        115                 120                 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
    130                 135                 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145                 150                 155                 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
                165                 170                 175

Thr Asp Arg Lys
            180
```

<210> 652
<211> 63
<212> PRT
<213> Homo sapiens

```
<400> 652
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
 1               5                  10                  15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
            20                  25                  30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
        35                  40                  45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
    50                  55                  60
```

<210> 653
<211> 63
<212> PRT
<213> Homo sapiens

```
<400> 653
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
 1               5                  10                  15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
            20                  25                  30
```

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 654
<211> 14
<212> PRT
<213> Homo sapiens

<400> 654
Ala Gly Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10

<210> 655
<211> 28
<212> PRT
<213> Homo sapiens

<400> 655
Ser Ala Asn Ser Asn Pro Ala Met Ala Pro Arg Glu Arg Lys Ala Gly
1 5 10 15

Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
20 25

<210> 656
<211> 28
<212> PRT
<213> Homo sapiens

<400> 656
Ser Ala Asn Ser Asn Pro Ala Met Ala Pro Arg Glu Arg Lys Ala Gly
1 5 10 15

Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
20 25

<210> 657
<211> 86
<212> PRT
<213> Homo sapiens

<400> 657
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg
20 25 30

Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
35 40 45

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys
50 55 60

Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln
65 70 75 80

Leu Glu Asn Tyr Cys Asn
85

<210> 658
<211> 63
<212> PRT
<213> Homo sapiens

<400> 658
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 659
<211> 63
<212> PRT
<213> Homo sapiens

<400> 659
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 660
<211> 63
<212> PRT
<213> Homo sapiens

<400> 660
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 661
<211> 63
<212> PRT
<213> Homo sapiens

<400> 661
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 662
<211> 63
<212> PRT
<213> Homo sapiens

<400> 662
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 663
<211> 62
<212> PRT
<213> Homo sapiens

<400> 663
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Lys Arg
20 25 30

Gly Gly Gly Pro Gly Arg Gly Lys Arg Gly Ile Val Glu Gln Cys Cys
35 40 45

Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 664
<211> 202
<212> PRT
<213> Homo sapiens

<400> 664
Met Leu Val Ala Gly Phe Leu Leu Ala Leu Pro Pro Ser Trp Ala Ala
1 5 10 15

Gly Ala Pro Arg Ala Gly Arg Arg Pro Ala Arg Pro Arg Gly Cys Ala
20 25 30

Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu Ala Ala
35 40 45

```
Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro Arg Glu
     50                  55                  60

Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala Asp Arg
 65                  70                  75                  80

Arg Phe Arg Pro Pro Thr Asn Leu Arg Ser Val Ser Pro Trp Ala Tyr
                 85                  90                  95

Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro Glu Ala
            100                 105                 110

Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu Glu Asp
        115                 120                 125

Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val Leu Arg
    130                 135                 140

Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu Ala Tyr
145                 150                 155                 160

Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu Lys Asp
                165                 170                 175

Ala Asp Ser Ile Asn Ser Ser Ile Asp Lys Gln Gly Ala Lys Leu Leu
            180                 185                 190

Leu Gly Pro Asn Asp Ala Pro Ala Gly Pro
        195                 200
```

<210> 665
<211> 14
<212> PRT
<213> Homo sapiens

<400> 665

```
Gly Gly Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
  1               5                  10
```

<210> 666
<211> 202
<212> PRT
<213> Homo sapiens

<400> 666

```
Met Leu Val Ala Gly Phe Leu Leu Ala Leu Pro Pro Ser Trp Ala Ala
  1               5                  10                  15

Gly Ala Pro Arg Ala Gly Arg Arg Pro Ala Arg Pro Arg Gly Cys Ala
            20                  25                  30

Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu Ala Ala
        35                  40                  45

Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro Arg Glu
     50                  55                  60

Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala Asp Arg
 65                  70                  75                  80

Arg Phe Arg Pro Pro Thr Asn Leu Arg Ser Val Ser Pro Trp Ala Tyr
                 85                  90                  95
```

```
Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro Glu Ala
            100                 105                 110

Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu Glu Asp
        115                 120                 125

Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val Leu Arg
    130                 135                 140

Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu Ala Tyr
145                 150                 155                 160

Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu Lys Asp
                165                 170                 175

Ala Asp Ser Ile Asn Ser Ser Ile Asp Lys Gln Gly Ala Lys Leu Leu
            180                 185                 190

Leu Gly Pro Asn Asp Ala Pro Ala Gly Pro
        195                 200
```

<210> 667
<211> 229
<212> PRT
<213> Homo sapiens

<400> 667

```
Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
  1               5                  10                  15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
             20                  25                  30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
         35                  40                  45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
     50                  55                  60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
 65                  70                  75                  80

Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro
                 85                  90                  95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
            100                 105                 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
        115                 120                 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
    130                 135                 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro
145                 150                 155                 160

Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
                165                 170                 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
            180                 185                 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
        195                 200                 205
```

```
Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
    210                 215                 220

Ser Gln Ser Glu Leu
225
```

<210> 668
<211> 406
<212> PRT
<213> Homo sapiens

<400> 668

```
Met Ser Gly Ala Pro Thr Ala Gly Ala Ala Leu Met Leu Cys Ala Ala
  1               5                  10                  15

Thr Ala Val Leu Leu Ser Ala Gln Gly Gly Pro Val Gln Ser Lys Ser
            20                  25                  30

Pro Arg Phe Ala Ser Trp Asp Glu Met Asn Val Leu Ala His Gly Leu
        35                  40                  45

Leu Gln Leu Gly Gln Gly Leu Arg Glu His Ala Glu Arg Thr Arg Ser
    50                  55                  60

Gln Leu Ser Ala Leu Glu Arg Arg Leu Ser Ala Cys Gly Ser Ala Cys
65                  70                  75                  80

Gln Gly Thr Glu Gly Ser Thr Asp Leu Pro Leu Ala Pro Glu Ser Arg
                85                  90                  95

Val Asp Pro Glu Val Leu His Ser Leu Gln Thr Gln Leu Lys Ala Gln
            100                 105                 110

Asn Ser Arg Ile Gln Gln Leu Phe His Lys Val Ala Gln Gln Gln Arg
        115                 120                 125

His Leu Glu Lys Gln His Leu Arg Ile Gln His Leu Gln Ser Gln Phe
    130                 135                 140

Gly Leu Leu Asp His Lys His Leu Asp His Glu Val Ala Lys Pro Ala
145                 150                 155                 160

Arg Arg Lys Arg Leu Pro Glu Met Ala Gln Pro Val Asp Pro Ala His
                165                 170                 175

Asn Val Ser Arg Leu His Arg Leu Pro Arg Asp Cys Gln Glu Leu Phe
            180                 185                 190

Gln Val Gly Glu Arg Gln Ser Gly Leu Phe Glu Ile Gln Pro Gln Gly
        195                 200                 205

Ser Pro Pro Phe Leu Val Asn Cys Lys Met Thr Ser Asp Gly Gly Trp
    210                 215                 220

Thr Val Ile Gln Arg Arg His Asp Gly Ser Val Asp Phe Asn Arg Pro
225                 230                 235                 240

Trp Glu Ala Tyr Lys Ala Gly Phe Gly Asp Pro His Gly Glu Phe Trp
                245                 250                 255

Leu Gly Leu Glu Lys Val His Ser Ile Thr Gly Asp Arg Asn Ser Arg
            260                 265                 270

Leu Ala Val Gln Leu Arg Asp Trp Asp Gly Asn Ala Glu Leu Leu Gln
        275                 280                 285
```

```
Phe Ser Val His Leu Gly Gly Glu Asp Thr Ala Tyr Ser Leu Gln Leu
    290                 295                 300

Thr Ala Pro Val Ala Gly Gln Leu Gly Ala Thr Thr Val Pro Pro Ser
305                 310                 315                 320

Gly Leu Ser Val Pro Phe Ser Thr Trp Asp Gln Asp His Asp Leu Arg
                325                 330                 335

Arg Asp Lys Asn Cys Ala Lys Ser Leu Ser Gly Gly Trp Trp Phe Gly
            340                 345                 350

Thr Cys Ser His Ser Asn Leu Asn Gly Gln Tyr Phe Arg Ser Ile Pro
        355                 360                 365

Gln Gln Arg Gln Lys Leu Lys Lys Gly Ile Phe Trp Lys Thr Trp Arg
    370                 375                 380

Gly Arg Tyr Tyr Pro Leu Gln Ala Thr Thr Met Leu Ile Gln Pro Met
385                 390                 395                 400

Ala Ala Glu Ala Ala Ser
                405
```

<210> 669
<211> 158
<212> PRT
<213> Homo sapiens

<400> 669

```
Met Ala Ser Arg Ser Met Arg Leu Leu Leu Leu Leu Ser Cys Leu Ala
  1               5                  10                  15

Lys Thr Gly Val Leu Gly Asp Ile Ile Met Arg Pro Ser Cys Ala Pro
            20                  25                  30

Gly Trp Phe Tyr His Lys Ser Asn Cys Tyr Gly Tyr Phe Arg Lys Leu
        35                  40                  45

Arg Asn Trp Ser Asp Ala Glu Leu Glu Cys Gln Ser Tyr Gly Asn Gly
    50                  55                  60

Ala His Leu Ala Ser Ile Leu Ser Leu Lys Glu Ala Ser Thr Ile Ala
65                  70                  75                  80

Glu Tyr Ile Ser Gly Tyr Gln Arg Ser Gln Pro Ile Trp Ile Gly Leu
                85                  90                  95

His Asp Pro Gln Lys Arg Gln Gln Trp Gln Trp Ile Asp Gly Ala Met
            100                 105                 110

Tyr Leu Tyr Arg Ser Trp Ser Gly Lys Ser Met Gly Gly Asn Lys His
        115                 120                 125

Cys Ala Glu Met Ser Ser Asn Asn Asn Phe Leu Thr Trp Ser Ser Asn
    130                 135                 140

Glu Cys Asn Lys Arg Gln His Phe Leu Cys Lys Tyr Arg Pro
145                 150                 155
```

<210> 670
<211> 63
<212> PRT
<213> Homo sapiens

<400> 670
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 671
<211> 63
<212> PRT
<213> Homo sapiens

<400> 671
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 672
<211> 63
<212> PRT
<213> Homo sapiens

<400> 672
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 673
<211> 63
<212> PRT
<213> Homo sapiens

<400> 673
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 674
<211> 76
<212> PRT
<213> Homo sapiens

<400> 674
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn Asp
50 55 60

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Val
65 70 75

<210> 675
<211> 180
<212> PRT
<213> Homo sapiens

<400> 675
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys

180

<210> 676
<211> 180
<212> PRT
<213> Homo sapiens

<400> 676
Met Lys Ser Ile Tyr Phe Val Ala Gly Leu Phe Val Met Leu Val Gln
1 5 10 15

Gly Ser Trp Gln Arg Ser Leu Gln Asp Thr Glu Glu Lys Ser Arg Ser
20 25 30

Phe Ser Ala Ser Gln Ala Asp Pro Leu Ser Asp Pro Asp Gln Met Asn
35 40 45

Glu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys
50 55 60

Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn
65 70 75 80

Thr Lys Arg Asn Arg Asn Asn Ile Ala Lys Arg His Asp Glu Phe Glu
85 90 95

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
100 105 110

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
115 120 125

Arg Arg Asp Phe Pro Glu Glu Val Ala Ile Val Glu Glu Leu Gly Arg
130 135 140

Arg His Ala Asp Gly Ser Phe Ser Asp Glu Met Asn Thr Ile Leu Asp
145 150 155 160

Asn Leu Ala Ala Arg Asp Phe Ile Asn Trp Leu Ile Gln Thr Lys Ile
165 170 175

Thr Asp Arg Lys
180

<210> 677
<211> 229
<212> PRT
<213> Homo sapiens

<400> 677
Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
1 5 10 15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
20 25 30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
35 40 45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
50 55 60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
65 70 75 80

```
Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro
                85                  90                  95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
           100                 105                 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
       115                 120                 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
   130                 135                 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro
145                 150                 155                 160

Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
                165                 170                 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
           180                 185                 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
       195                 200                 205

Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
   210                 215                 220

Ser Gln Ser Glu Leu
225
```

<210> 678
<211> 229
<212> PRT
<213> Homo sapiens

<400> 678

```
Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
  1               5                  10                  15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
            20                  25                  30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
        35                  40                  45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
    50                  55                  60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
65                  70                  75                  80

Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro
                85                  90                  95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
           100                 105                 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
       115                 120                 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
   130                 135                 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro
145                 150                 155                 160
```

```
Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
                165                 170                 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
            180                 185                 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
        195                 200                 205

Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
    210                 215                 220

Ser Gln Ser Glu Leu
225
```

<210> 679
<211> 229
<212> PRT
<213> Homo sapiens

<400> 679

```
Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
  1               5                  10                  15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
            20                  25                  30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
        35                  40                  45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
    50                  55                  60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
65                  70                  75                  80

Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro
                85                  90                  95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
            100                 105                 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
        115                 120                 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
    130                 135                 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro
145                 150                 155                 160

Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
                165                 170                 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
            180                 185                 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
        195                 200                 205

Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
    210                 215                 220

Ser Gln Ser Glu Leu
225
```

<210> 680
<211> 229
<212> PRT
<213> Homo sapiens

<400> 680
Met Asp Leu Leu Gln Phe Leu Ala Phe Leu Phe Val Leu Leu Leu Ser
1 5 10 15

Gly Met Gly Ala Thr Gly Thr Leu Arg Thr Ser Leu Asp Pro Ser Leu
20 25 30

Glu Ile Tyr Lys Lys Met Phe Glu Val Lys Arg Arg Glu Gln Leu Leu
35 40 45

Ala Leu Lys Asn Leu Ala Gln Leu Asn Asp Ile His Gln Gln Tyr Lys
50 55 60

Ile Leu Asp Val Met Leu Lys Gly Leu Phe Lys Val Leu Glu Asp Ser
65 70 75 80

Arg Thr Val Leu Thr Ala Ala Asp Val Leu Pro Asp Gly Pro Phe Pro
85 90 95

Gln Asp Glu Lys Leu Lys Asp Ala Phe Ser His Val Val Glu Asn Thr
100 105 110

Ala Phe Phe Gly Asp Val Val Leu Arg Phe Pro Arg Ile Val His Tyr
115 120 125

Tyr Phe Asp His Asn Ser Asn Trp Asn Leu Leu Ile Arg Trp Gly Ile
130 135 140

Ser Phe Cys Asn Gln Thr Gly Val Phe Asn Gln Gly Pro His Ser Pro
145 150 155 160

Ile Leu Ser Leu Met Ala Gln Glu Leu Gly Ile Ser Glu Lys Asp Ser
165 170 175

Asn Phe Gln Asn Pro Phe Lys Ile Asp Arg Thr Glu Phe Ile Pro Ser
180 185 190

Thr Asp Pro Phe Gln Lys Ala Leu Arg Glu Glu Glu Lys Arg Arg Lys
195 200 205

Lys Glu Glu Lys Arg Lys Glu Ile Arg Lys Gly Pro Arg Ile Ser Arg
210 215 220

Ser Gln Ser Glu Leu
225

<210> 681
<211> 244
<212> PRT
<213> Homo sapiens

<400> 681
Met Leu Leu Leu Gly Ala Val Leu Leu Leu Ala Leu Pro Gly His
1 5 10 15

Asp Gln Glu Thr Thr Thr Gln Gly Pro Gly Val Leu Leu Pro Leu Pro
20 25 30

Lys Gly Ala Cys Thr Gly Trp Met Ala Gly Ile Pro Gly His Pro Gly

```
         35                  40                  45

His Asn Gly Ala Pro Gly Arg Asp Gly Arg Asp Gly Thr Pro Gly Glu
     50                  55                  60

Lys Gly Glu Lys Gly Asp Pro Gly Leu Ile Gly Pro Lys Gly Asp Ile
 65                  70                  75                  80

Gly Glu Thr Gly Val Pro Gly Ala Glu Gly Pro Arg Gly Phe Pro Gly
                 85                  90                  95

Ile Gln Gly Arg Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg
            100                 105                 110

Ser Ala Phe Ser Val Gly Leu Glu Thr Tyr Val Thr Ile Pro Asn Met
        115                 120                 125

Pro Ile Arg Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp
    130                 135                 140

Gly Ser Thr Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe
145                 150                 155                 160

Ala Tyr His Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe
                165                 170                 175

Lys Lys Asp Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn
            180                 185                 190

Asn Val Asp Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly
        195                 200                 205

Asp Gln Val Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu
    210                 215                 220

Tyr Ala Asp Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr
225                 230                 235                 240

His Asp Thr Asn
```

<210> 682
<211> 244
<212> PRT
<213> Homo sapiens

```
<400> 682
Met Leu Leu Leu Gly Ala Val Leu Leu Leu Leu Ala Leu Pro Gly His
  1               5                  10                  15

Asp Gln Glu Thr Thr Thr Gln Gly Pro Gly Val Leu Leu Pro Leu Pro
             20                  25                  30

Lys Gly Ala Cys Thr Gly Trp Met Ala Gly Ile Pro Gly His Pro Gly
         35                  40                  45

His Asn Gly Ala Pro Gly Arg Asp Gly Arg Asp Gly Thr Pro Gly Glu
     50                  55                  60

Lys Gly Glu Lys Gly Asp Pro Gly Leu Ile Gly Pro Lys Gly Asp Ile
 65                  70                  75                  80

Gly Glu Thr Gly Val Pro Gly Ala Glu Gly Pro Arg Gly Phe Pro Gly
                 85                  90                  95

Ile Gln Gly Arg Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg
```

100 105 110

Ser Ala Phe Ser Val Gly Leu Glu Thr Tyr Val Thr Ile Pro Asn Met
115 120 125

Pro Ile Arg Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp
130 135 140

Gly Ser Thr Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe
145 150 155 160

Ala Tyr His Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe
165 170 175

Lys Lys Asp Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn
180 185 190

Asn Val Asp Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly
195 200 205

Asp Gln Val Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu
210 215 220

Tyr Ala Asp Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr
225 230 235 240

His Asp Thr Asn

<210> 683
<211> 244
<212> PRT
<213> Homo sapiens

<400> 683
Met Leu Leu Leu Gly Ala Val Leu Leu Leu Ala Leu Pro Gly His
1 5 10 15

Asp Gln Glu Thr Thr Thr Gln Gly Pro Gly Val Leu Leu Pro Leu Pro
20 25 30

Lys Gly Ala Cys Thr Gly Trp Met Ala Gly Ile Pro Gly His Pro Gly
35 40 45

His Asn Gly Ala Pro Gly Arg Asp Gly Arg Asp Gly Thr Pro Gly Glu
50 55 60

Lys Gly Glu Lys Gly Asp Pro Gly Leu Ile Gly Pro Lys Gly Asp Ile
65 70 75 80

Gly Glu Thr Gly Val Pro Gly Ala Glu Gly Pro Arg Gly Phe Pro Gly
85 90 95

Ile Gln Gly Arg Lys Gly Glu Pro Gly Glu Gly Ala Tyr Val Tyr Arg
100 105 110

Ser Ala Phe Ser Val Gly Leu Glu Thr Tyr Val Thr Ile Pro Asn Met
115 120 125

Pro Ile Arg Phe Thr Lys Ile Phe Tyr Asn Gln Gln Asn His Tyr Asp
130 135 140

Gly Ser Thr Gly Lys Phe His Cys Asn Ile Pro Gly Leu Tyr Tyr Phe
145 150 155 160

Ala Tyr His Ile Thr Val Tyr Met Lys Asp Val Lys Val Ser Leu Phe
165 170 175

```
Lys Lys Asp Lys Ala Met Leu Phe Thr Tyr Asp Gln Tyr Gln Glu Asn
            180                 185                 190

Asn Val Asp Gln Ala Ser Gly Ser Val Leu Leu His Leu Glu Val Gly
        195                 200                 205

Asp Gln Val Trp Leu Gln Val Tyr Gly Glu Gly Glu Arg Asn Gly Leu
    210                 215                 220

Tyr Ala Asp Asn Asp Asn Asp Ser Thr Phe Thr Gly Phe Leu Leu Tyr
225                 230                 235                 240

His Asp Thr Asn
```

<210> 684
<211> 83
<212> PRT
<213> Homo sapiens

<400> 684

```
Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
  1               5                  10                  15

Ser Val Ile Asn Tyr Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp
            20                  25                  30

Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp
        35                  40                  45

Leu Val Lys Gly Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser
    50                  55                  60

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
65                  70                  75                  80

Lys Gly Arg
```

<210> 685
<211> 145
<212> PRT
<213> Homo sapiens

<400> 685

```
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
  1               5                  10                  15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
            20                  25                  30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
        35                  40                  45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
    50                  55                  60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65                  70                  75                  80

Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser
                85                  90                  95

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
            100                 105                 110
```

```
Lys Gly Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr
        115                 120                 125

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly
    130                 135                 140

Arg
145
```

<210> 686
<211> 77
<212> PRT
<213> Homo sapiens

<400> 686

```
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
  1               5                  10                  15

Ala His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
            20                  25                  30

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His
        35                  40                  45

Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
    50                  55                  60

Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
65                  70                  75
```

<210> 687
<211> 145
<212> PRT
<213> Homo sapiens

<400> 687

```
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
  1               5                  10                  15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
            20                  25                  30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
        35                  40                  45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
    50                  55                  60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65                  70                  75                  80

Ser Leu Asp Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser
                85                  90                  95

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
            100                 105                 110

Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr
        115                 120                 125

Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly
    130                 135                 140
```

Arg
145

<210> 688
<211> 83
<212> PRT
<213> Homo sapiens

<400> 688
Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
1 5 10 15

Ser Val Ile Asn Tyr Lys Arg His Gly Glu Gly Thr Phe Thr Ser Asp
20 25 30

Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp
35 40 45

Leu Val Lys Gly Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser
50 55 60

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
65 70 75 80

Lys Gly Arg

<210> 689
<211> 77
<212> PRT
<213> Homo sapiens

<400> 689
Met Phe Lys Ser Val Val Tyr Ser Ile Leu Ala Ala Ser Leu Ala Asn
1 5 10 15

Ala His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu
20 25 30

Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His
35 40 45

Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
50 55 60

Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
65 70 75

<210> 690
<211> 31
<212> PRT
<213> Homo sapiens

<400> 690
Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro
1 5 10 15

Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln
20 25 30

<210> 691

<211> 131
<212> PRT
<213> Homo sapiens

<400> 691
Val Pro Ala Pro Lys Val Pro Ile Lys Met Gln Val Lys His Trp Pro
1 5 10 15

Ser Glu Gln Asp Pro Glu Lys Ala Trp Gly Ala Arg Val Val Glu Pro
20 25 30

Pro Glu Lys Asp Asp Gln Leu Val Val Leu Phe Pro Val Gln Lys Pro
35 40 45

Lys Leu Leu Thr Thr Glu Glu Lys Pro Arg Gly Gln Gly Arg Gly Pro
50 55 60

Ile Leu Pro Gly Thr Lys Ala Trp Met Glu Thr Glu Asp Thr Leu Gly
65 70 75 80

Arg Val Leu Ser Pro Glu Pro Asp His Asp Ser Leu Tyr His Pro Pro
85 90 95

Pro Glu Glu Asp Gln Gly Glu Glu Arg Pro Arg Leu Trp Val Met Pro
100 105 110

Asn His Gln Val Leu Leu Gly Pro Glu Glu Asp Gln Asp His Ile Tyr
115 120 125

His Pro Gln
130

<210> 692
<211> 36
<212> PRT
<213> Homo sapiens

<400> 692
Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 693
<211> 34
<212> PRT
<213> Homo sapiens

<400> 693
Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
1 5 10 15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 694
<211> 34
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<400> 694
Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
1 5 10 15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 695
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<400> 695
Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
1 5 10 15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 696
<211> 63
<212> PRT
<213> Homo sapiens

<400> 696
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55 60

<210> 697
<211> 63
<212> PRT
<213> Homo sapiens

<400> 697
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Gly Tyr
20 25 30

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Glu Gln Cys
35 40 45

Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn

50 55 60

<210> 698
<211> 30
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<213> Homo sapiens

<400> 698
His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1 5 10 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
20 25 30

<210> 699
<211> 389
<212> PRT
<213> Homo sapiens

<400> 699
Met Leu Glu Glu Pro Arg Pro Arg Pro Pro Pro Ser Gly Leu Ala Gly
1 5 10 15

Leu Leu Phe Leu Ala Leu Cys Ser Arg Ala Leu Ser Asn Glu Ile Leu
20 25 30

Gly Leu Lys Leu Pro Gly Glu Pro Pro Leu Thr Ala Asn Thr Val Cys
35 40 45

Leu Thr Leu Ser Gly Leu Ser Lys Arg Gln Leu Asp Leu Cys Leu Arg
50 55 60

Asn Pro Asp Val Thr Ala Ser Ala Leu Gln Gly Leu His Ile Ala Val
65 70 75 80

His Glu Cys Gln His Gln Leu Arg Asp Gln Arg Trp Asn Cys Ser Ala
85 90 95

Leu Glu Gly Gly Gly Arg Leu Pro His His Ser Ala Ile Leu Lys Arg
100 105 110

Gly Phe Arg Glu Ser Ala Phe Ser Phe Ser Met Leu Ala Ala Gly Val
115 120 125

Met His Ala Val Ala Thr Ala Cys Ser Leu Gly Lys Leu Val Ser Cys
130 135 140

Gly Cys Gly Trp Lys Gly Ser Gly Glu Gln Asp Arg Leu Arg Ala Lys
145 150 155 160

Leu Leu Gln Leu Gln Ala Leu Ser Arg Gly Lys Ser Phe Pro His Ser
165 170 175

Leu Pro Ser Pro Gly Pro Gly Ser Ser Pro Ser Pro Gly Pro Gln Asp
180 185 190

Thr Trp Glu Trp Gly Gly Cys Asn His Asp Met Asp Phe Gly Glu Lys
195 200 205

Phe Ser Arg Asp Phe Leu Asp Ser Arg Glu Ala Pro Arg Asp Ile Gln
210 215 220

Ala Arg Met Arg Ile His Asn Asn Arg Val Gly Arg Gln Val Val Thr
225 230 235 240

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Glu Asn Leu Lys Arg Lys Cys Lys Cys His Gly Thr Ser Gly Ser Cys
                245                 250                 255

Gln Phe Lys Thr Cys Trp Arg Ala Ala Pro Glu Phe Arg Ala Val Gly
            260                 265                 270

Ala Ala Leu Arg Glu Arg Leu Gly Arg Ala Ile Phe Ile Asp Thr His
        275                 280                 285

Asn Arg Asn Ser Gly Ala Phe Gln Pro Arg Leu Arg Pro Arg Arg Leu
    290                 295                 300

Ser Gly Glu Leu Val Tyr Phe Glu Lys Ser Pro Asp Phe Cys Glu Arg
305                 310                 315                 320

Asp Pro Thr Met Gly Ser Pro Gly Thr Arg Gly Arg Ala Cys Asn Lys
                325                 330                 335

Thr Ser Arg Leu Leu Asp Gly Cys Gly Ser Leu Cys Cys Gly Arg Gly
            340                 345                 350

His Asn Val Leu Arg Gln Thr Arg Val Glu Arg Cys His Cys Arg Phe
        355                 360                 365

His Trp Cys Cys Tyr Val Leu Cys Asp Glu Cys Lys Val Thr Glu Trp
    370                 375                 380

Val Asn Val Cys Lys
385
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<210> 700
<211> 68
<212> PRT
<213> Homo sapiens

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Glu Ala Ala Leu Gly Leu Glu Ala Glu Asp Leu Gln Val Gly Gln Val
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Glu Leu Gly Gly Gly Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu
             20                  25                  30

Glu Gly Ser Leu Gln Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu
         35                  40                  45

Leu Gly Gly Gly Pro Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu
     50                  55                  60

Gly Ser Leu Gln
 65
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<210> 701
<211> 58
<212> PRT
<213> Homo sapiens

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<400> 701
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
  1               5                  10                  15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Glu Ala
             20                  25                  30

Glu Asp Leu Gln Val Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
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35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55

<210> 702
<211> 58
<212> PRT
<213> Homo sapiens

<400> 702
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Glu Ala
20 25 30

Glu Asp Leu Gln Val Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
35 40 45

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
50 55

<210> 703
<211> 116
<212> PRT
<213> Homo sapiens

<400> 703
Met Glu Ser Ser Arg Val Arg Leu Leu Pro Leu Leu Gly Ala Ala Leu
1 5 10 15

Leu Leu Met Leu Pro Leu Leu Gly Thr Arg Ala Gln Glu Asp Ala Glu
20 25 30

Leu Gln Pro Arg Ala Leu Asp Ile Tyr Ser Ala Val Asp Asp Ala Ser
35 40 45

His Glu Lys Glu Leu Ile Glu Ala Leu Gln Glu Val Leu Lys Lys Leu
50 55 60

Lys Ser Lys Arg Val Pro Ile Tyr Glu Lys Lys Tyr Gly Gln Val Pro
65 70 75 80

Met Cys Asp Ala Gly Glu Gln Cys Ala Val Arg Lys Gly Ala Arg Ile
85 90 95

Gly Lys Leu Cys Asp Cys Pro Arg Gly Thr Ser Cys Asn Ser Phe Leu
100 105 110

Leu Lys Cys Leu
115

<210> 704
<211> 131
<212> PRT
<213> Homo sapiens

<400> 704
Val Pro Ala Pro Lys Val Pro Ile Lys Met Gln Val Lys His Trp Pro
1 5 10 15

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Ser Glu Gln Asp Pro Glu Lys Ala Trp Gly Ala Arg Val Val Glu Pro
            20                  25                  30

Pro Glu Lys Asp Asp Gln Leu Val Val Leu Phe Pro Val Gln Lys Pro
        35                  40                  45

Lys Leu Leu Thr Thr Glu Glu Lys Pro Arg Gly Gln Gly Arg Gly Pro
    50                  55                  60

Ile Leu Pro Gly Thr Lys Ala Trp Met Glu Thr Glu Asp Thr Leu Gly
65                  70                  75                  80

Arg Val Leu Ser Pro Glu Pro Asp His Asp Ser Leu Tyr His Pro Pro
                85                  90                  95

Pro Glu Glu Asp Gln Gly Glu Glu Arg Pro Arg Leu Trp Val Met Pro
            100                 105                 110

Asn His Gln Val Leu Leu Gly Pro Glu Glu Asp Gln Asp His Ile Tyr
        115                 120                 125

His Pro Gln
    130
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<210> 705
<211> 34
<212> PRT
<213> Homo sapiens

<400> 705
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Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
  1               5                  10                  15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
            20                  25                  30

Arg Tyr
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<210> 706
<211> 34
<212> PRT
<213> Homo sapiens

<400> 706
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Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
  1               5                  10                  15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
            20                  25                  30

Arg Tyr
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<210> 707
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<212> DNA
<213> Homo sapiens

<400> 707
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<210> 708
<211> 26
<212> DNA

<213> Homo sapiens

<400> 708
cttcaaatgg acactgctga agatac 26

<210> 709
<211> 20
<212> DNA
<213> Homo sapiens

<400> 709
cctgctttgc cgaggagggt 20

<210> 710
<211> 28
<212> DNA
<213> Homo sapiens

<400> 710
taaaatacac accgagattc atcaactc 28

<210> 711
<211> 33
<212> DNA
<213> Homo sapiens

<400> 711
aggagcgtcg acaaaagatt cgttaaccaa cac 33

<210> 712
<211> 26
<212> DNA
<213> Homo sapiens

<400> 712
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<210> 713
<211> 20
<212> DNA
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<400> 713
cctgctttgc cgaggagggt 20

<210> 714
<211> 28
<212> DNA
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<400> 714
taaaatacac accgagattc atcaactc 28

<210> 715
<211> 29
<212> DNA
<213> Homo sapiens

<400> 715
gcattcgtta accaacactt gtgtggttc 29

<210> 716
<211> 28
<212> DNA
<213> Homo sapiens

<400> 716

aatctttaaa tcgatgagca acctcact 28

<210> 717
<211> 29
<212> DNA
<213> Homo sapiens

<400> 717
gcagttaacc aacacttgtg tggttctca 29

<210> 718
<211> 28
<212> DNA
<213> Homo sapiens

<400> 718
aatctttaaa tcgatgagca acctcact 28

<210> 719
<211> 33
<212> DNA
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<400> 719
gcattcgtta accaacactt gtgtggttct cac 33

<210> 720
<211> 59
<212> DNA
<213> Homo sapiens

<400> 720
ctttaaatcg atgagcaacc tcactcttgt gtgcatcgtt acagtagttt tccaattgg 59

<210> 721
<211> 33
<212> DNA
<213> Homo sapiens

<400> 721
gcattcgtta accaacactt gtgtggttct cac 33

<210> 722
<211> 59
<212> DNA
<213> Homo sapiens

<400> 722
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<210> 723
<211> 54
<212> DNA
<213> Homo sapiens

<400> 723
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<210> 724
<211> 60
<212> DNA
<213> Homo sapiens

<400> 724
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<210> 725

<211> 20
<212> DNA
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<400> 725
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<210> 726
<211> 25
<212> DNA
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<400> 726
agactttaaa tcgatgagca acctc 25

<210> 727
<211> 35
<212> DNA
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<400> 727
aagctgcctt aggcttagct ggttgtaaga acttc 35

<210> 728
<211> 39
<212> DNA
<213> Homo sapiens

<400> 728
cggccggggc gcgccttaac aagaagtgaa agtcttcca 39

<210> 729
<211> 206
<212> DNA
<213> Homo sapiens

<400> 729
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gctggttgta agaacgcgcg cgtcgacaaa agatctgcta actctaaccc agctatggct 120
ccaagagaaa gaaaggctgg ttgtaagaac gcgcgcgtcg acaaaagatc tgctaactct 180
aacccagcta tggctccaag agaaag 206

<210> 730
<211> 60
<212> DNA
<213> Homo sapiens

<400> 730
gcgcgcgcat cgatgagcaa cctcactctt gtgtgcatca caagaagtga aagtcttcca 60

<210> 731
<211> 39
<212> DNA
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<400> 731
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<210> 732
<211> 39
<212> DNA
<213> Homo sapiens

<400> 732
cggccggggc gcgccttaac aagaagtgaa agtcttcca 39

<210> 733
<211> 33

<212> DNA
<213> Homo sapiens

<400> 733
gcattcgtta accaacactt gtgtggttct cac 33

<210> 734
<211> 59
<212> DNA
<213> Homo sapiens

<400> 734
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<210> 735
<211> 60
<212> DNA
<213> Homo sapiens

<400> 735
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<210> 736
<211> 27
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<400> 736
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<210> 737
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<400> 737
gctaaaccta attcgaacaa gcaaag 26

<210> 738
<211> 27
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<400> 738
ctgagcaaag gcaatcaaca ccaaggc 27

<210> 739
<211> 38
<212> DNA
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<400> 739
tagctattcg aaaacaagca aagatgaagt gggtaagc 38

<210> 740
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<212> DNA
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<400> 740
tatcaaatgc ggccgcttat aagcctaagg cagcttgac 39

<210> 741
<211> 32
<212> DNA
<213> Homo sapiens

<400> 741
aggagcgtcg acaaaagagc cccgaggcgg gc 32

<210> 742
<211> 52
<212> DNA
<213> Homo sapiens

<400> 742
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<210> 743
<211> 30
<212> DNA
<213> Homo sapiens

<400> 743
gcgcgcgtcg acaaaagagg tggttgtaag 30

<210> 744
<211> 60
<212> DNA
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<400> 744
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<210> 745
<211> 31
<212> DNA
<213> Homo sapiens

<400> 745
aagctgcctt aggcttagcc ccgagggcgg a 31

<210> 746
<211> 51
<212> DNA
<213> Homo sapiens

<400> 746
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<210> 747
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<212> DNA
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<400> 747
aagctgcctt aggcttaatg gaccttcttc aa 32

<210> 748
<211> 51
<212> DNA
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<212> DNA
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<212> DNA
<213> Homo sapiens

<400> 753
cgcggatccc aggcctttgt gaaccaacac ctgtg 35

<210> 754
<211> 71
<212> DNA
<213> Homo sapiens

<400> 754
ctttaaatcg atgagcaacc tcactcttgt gtgcatcgtt gcagtagttc tccagctggt 60
agagggagca g 71

<210> 755
<211> 69
<212> DNA
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<400> 755
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ctctctacc 69

<210> 756
<211> 70
<212> DNA
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<400> 756
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acagcattgt 70

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<211> 25
<212> DNA
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gagtccaatt agcttcatcg ccaat 25

<210> 758
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agactttaaa tcgatgagca acctc 25

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<400> 760
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<400> 761
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caagagattc gttaaccaac acttgt 86

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<400> 762
ctcccaaatc tttaaatcga tgagcaa 27

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gcacacggtg aaggtacttt cacttc 26

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<210> 772
<211> 40
<212> DNA
<213> Homo sapiens

<400> 772
atctaaggcg cgccctataa ctcagactgg gatctggaga 40

<210> 773
<211> 37
<212> DNA
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<400> 773
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<400> 774
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<210> 778
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<212> DNA
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<400> 778
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<212> DNA
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<400> 780
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<210> 781
<211> 40
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<400> 781
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<210> 782
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<210> 783

<211> 38
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<400> 785
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<400> 786
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<400> 796
ctcccaaatc tttaaatcga tgagcaa 27

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<210> 798
<211> 74
<212> DNA
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ctggaccacc accc 74

<210> 799
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20 25 30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
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Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
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Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
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Thr Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
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Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala
35 40 45

Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg His Gly Glu Gly Thr
50 55 60

Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu
65 70 75 80

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85 90 95

Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val
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115 120 125

Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala
130 135 140

Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
145 150 155 160

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165 170 175

Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
180 185 190

Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu
195 200 205

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210 215 220

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225 230 235 240

Pro Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln
245 250 255

Cys Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp
260 265 270

Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys
275 280 285

Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala

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305 310 315 320

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325 330 335

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
340 345 350

Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys
355 360 365

Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His
370 375 380

Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu
385 390 395 400

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405 410 415

Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val
420 425 430

Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys
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Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala
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Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn
465 470 475 480

Cys Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile
485 490 495

Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu
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Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr
515 520 525

Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala
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Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu
545 550 555 560

His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys
565 570 575

Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
580 585 590

Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys
595 600 605

Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His
610 615 620

Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe
625 630 635 640

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Gln Met His Phe Ser Gly His Leu Ala Phe Leu Leu Ser Thr Gly Glu
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Ile Thr Phe Val Ser Ser Leu Val Lys Asn Ser Leu Thr Ala Tyr Gln
                85                  90                  95

Tyr Ile Trp Ile Gly Leu His Asp Pro Ser His Gly Thr Leu Pro Asn
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Gly Ser Gly Trp Lys Trp Ser Ser Ser Asn Val Leu Thr Phe Tyr Asn
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Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
20 25 30

Gly Gly Pro Gly Lys Arg
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60/378,950	10 May 2002 (10.05.2002)	US
60/398,008	24 July 2002 (24.07.2002)	US
60/402,131	9 August 2002 (09.08.2002)	US
60/402,708	13 August 2002 (13.08.2002)	US
60/411,355	18 September 2002 (18.09.2002)	US
60/414,984	2 October 2002 (02.10.2002)	US
60/417,611	11 October 2002 (11.10.2002)	US
60/420,246	23 October 2002 (23.10.2002)	US
60/423,623	5 November 2002 (05.11.2002)	US

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(74) Agent: **WALES, Michele, M.**; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *with international search report*
— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

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26 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ALBUMIN FUSION PROTEINS

(57) Abstract: The present invention encompasses albumin fusion proteins. Nucleic acid molecules encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Additionally the present invention encompasses pharmaceutical compositions comprising albumin fusion proteins and methods of treating or preventing diseases, disorders or conditions related to diabetes mellitus using albumin fusion proteins of the invention.

WO 2003/059934 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40892

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07K 14/00
US CL : 530/350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, Dialog, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YU et al. A newly identified member of tumor necrosis factor receptor superfamily (TR6) suppresses LIGHT-mediated apoptosis. Journal of Biological Chemishtry. 14 May 1999, Vol. 274, No. 20, pages 13733-13736.	1-21
A	US 5,876,969 A (FLEER et al.) 02 March 1999 (02.03.99).	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search
12 August 2003 (12.08.2003)

Date of mailing of the international search report
02 SEP 2003

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40892

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-21, drawn to fusion protein #1, SEQ ID NO: 70

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/40892

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups 1-161, claim(s) 1-21, drawn to albumen fusion proteins NO: 1 to NO: 161, respectively, from Table 2.

Group 162-322, claim(s) 22, drawn to method of treating disease via administration of albumen fusion proteins NO: 1 to NO: 161, respectively, from Table 2.

Group 323-483, claim(s) 23, drawn to method of treating metabolic disorders via administration of albumen fusion proteins NO: 1 to NO: 161, respectively, from Table 2.

Group 484-644, claim(s) 24-33 and 35, drawn to method of treating diabetes via administration of albumen fusion proteins NO: 1 to NO: 161, respectively, from Table 2.

Group 645-805, claim(s) 34 and 36, drawn to method of treating obesity via administration of albumen fusion proteins NO: 1 to NO: 161, respectively, from Table 2.

Group 806-966, claim(s) 37, drawn to method of extending the shelf life of albumen fusion proteins NO: 1 to NO: 161, respectively, from Table 2.

Group 967-1127, claim(s) 38-40, drawn to nucleic acid encoding albumen fusion proteins NO: 1 to NO: 161, respectively, from Table 2.

The inventions listed as Groups 1-1127 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the albumen fusion proteins NO:1 differs in structure and function from albumen fusion proteins NO: 2-NO:161 because the attached therapeutic protein is different for each fusion protein as set forth in Table 2.Further, the fusion proteins comprising an amino acid from therapeutic protein X and an amino acid from albumen reads on any peptide sequence and therefore the claimed fusion protein is not novel and does not represent a special technical feature. See, for example, Habermann et al. (US Patent 5,496,924) who teach fusion proteins comprising an Asp-Pro linker, wherein Asp and Pro are considered to be fragments of therapeutic protein X and albumen. Therefore, the groups do not relate to a single general inventive concept.

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